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The Insulin-Like Growth Factors and In Utero Growth

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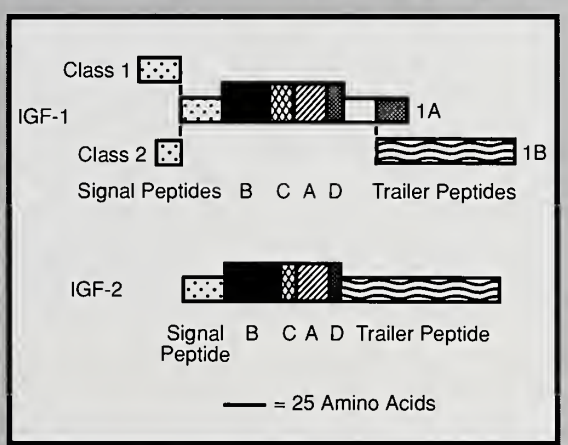
The well-described capacity of the insulin-like growth factors (IGFs; IGF-1 and IGF-2) to stimulate cellular proliferation has long made them attractive candidates for a role in the regulation of embryonic and fetal growth (see Figure 1).[1,2] More recent evidence that the IGFs can also stimulate differentiation and/or differentiated cell function in some cultured cells enhanced their potential importance in utero. Claims of a functional role for IGFs in development have been further strengthened by findings that they, as well as their cell surface receptors, are expressed in a variety of tissues early in embryonic life. Despite an impressive body of evidence, derived from many lines of investigation, there remained no direct evidence of a role for the IGFs in utero until the last year. The finding of significant fetal growth retardation in mice with a marked reduction in IGF-2 expression (> 90%) resulting from a hemizygous disruption of the IGF-2 gene (accomplished by homologous recombination of a normal allele and an artificial fusion gene) provides direct confirmation that IGF-2 is a stimulator of fetal growth in mice.[3] Comparable experiments involving the IGF-1 gene have not yet been reported, but a number of in vivo studies have demonstrated the capacity of IGF-1 to stimulate somatic and linear growth in mice postnatally, including during the suckling period, a time that is analogous in many ways to the third trimester of human gestation.[4]

Figure 1
Insulin-Like Growth Factor Precursors



IGF-1 (top) and IGF-2 (bottom) precursor proteins are schematically depicted, with the large blocks representing the mature proteins. Analogous or homologous domains of the precursors are labeled and drawn with the same designs. IGF-1 has at least 2 alternative signal peptides and 2 trailer peptides that differ at their carboxy-terminal ends.

In This Issue

Letter From the Editor

Five years ago, Dr. A. Joseph D'Ercole wrote an excellent article for *GGH*, which was entitled "Fetal Growth and Development: A Brief Survey of Cellular Mechanisms." Five years ago, Dr. Joseph Warshaw also wrote an excellent article, which was entitled "Perspectives on Intrauterine Growth Retardation." You may wish to review these articles as you read an update of each of these topics by these authors in this issue of *GGH*. Both updates are excellent.

Terminology regarding intrauterine growth retardation (IUGR) and small-for-gestational age (SGA) infants has been exceedingly confusing. It is time that these terms be clarified. Clarification will enhance our diagnostic and investigative approach to IUGR and SGA babies. Dr. Warshaw has taken a bounding step forward to clarify these terms. You as a reader are invited to write and express your opinion.

Several abstracts in this issue also deal with IUGR and low birth weight. These were selected because of the focus on fetal growth in this, the first issue of the eighth volume of *GGH*.

Robert M. Blizzard, MD

POTENTIAL ACTIONS OF THE INSULIN-LIKE GROWTH FACTORS IN UTERO

What developmental events might be stimulated by IGFs in utero? Studies of the actions of the IGFs in cultured cells suggest myriad possibilities. Both IGF-1 and IGF-2 are capable of stimulating cellular replication in a variety of cultured cells, including those derived from the fetus. The finding that a near absence of IGF-2 expression in mice with a disrupted IGF-2 gene results in fetal growth retardation without apparent morphologic abnormalities suggests that stimulation of mitosis is a major function of IGF-2 in utero. A number of studies, however, indicate that IGFs, especially IGF-1, also are capable of inducing differentiation and/or differentiated cell function. Examples of the former are the induction of myotubule formation in myoblasts,[5] lens fiber cell formation in chick lens epithelium, and adipocyte differentiation in preadipocyte cell lines by IGF-1. The capacity of IGFs to induce differentiated cell function encompasses the stimulation of glycogen synthesis in fetal rat hepatocytes by IGF-1, type I collagen formation in cartilage by IGF-1 and IGF-2, and prolactin synthesis in human placenta by IGF-1.

The early embryonic expression of IGFs and their receptors lends credence to the possibility that IGFs participate in stimulating a variety of developmental events. But how can such divergent responses be attributed to IGFs? While there is no certain answer to this question, it is likely that different mechanisms mediate and modulate IGF actions in a cell type-specific and developmental stage-specific fashion. In other words, the actions of IGFs may be determined in large part by the nature of the target cell, the receptor it expresses, and the signaling mechanisms triggered by the IGF-receptor interaction. IGF actions will also be influenced by the actions of other regulatory agents that can either alter or determine the cellular response to IGFs, and by the presence of specific IGF-binding proteins (IGFBPs) that can modulate IGF action.[6] Finally, in the case of IGF-1, different precursor forms could confer different biologic responses (see Figure 1, page 1).[7]

EXPRESSION OF THE INSULIN-LIKE GROWTH FACTORS IN UTERO

Using the polymerase chain reaction, transcripts for IGF-2 have been detected in 2-cell preimplantation mouse embryos, and have been localized by in situ hybridization in placental components as early as day 18 of gestation in humans.[8-15] As gestation progresses, IGF-2 transcripts become more abundant and are expressed in many embryonic and extraembryonic tissues. IGF-2 expression occurs in most tissues of mesodermal origin, especially those that are actively undergoing differentiation, such as somite derivatives, muscle, and head mesenchyma; but it is also strongly expressed in some cells of ectodermal (eg, choroid plexus) and endodermal (eg, liver and bronchi) origin. The onset of IGF-1 expression is later, possibly beginning shortly after implantation at approximately 7 to 8 days of gestation in the mouse, and clearly occurring in early organogenesis. IGF-1 transcripts can be localized in undifferentiated mesenchyma, especially that which surrounds spouting nerves and areas of active remodeling, such as cardiac outflow tracts. Later IGF-1 expression is most marked in a variety of connective tissues, such as those surrounding muscle and cartilage. Because there are limitations in detection of RNA by in situ hybridization and apparently rapid developmental changes in IGF expression, it is unlikely that all cell types expressing IGFs have been defined. The widespread expression of IGFs, including the time prior to circulatory system development, strongly supports the concept that during embryogenesis IGFs can act locally on or near their cells of synthesis, ie, in an autocrine or paracrine manner.

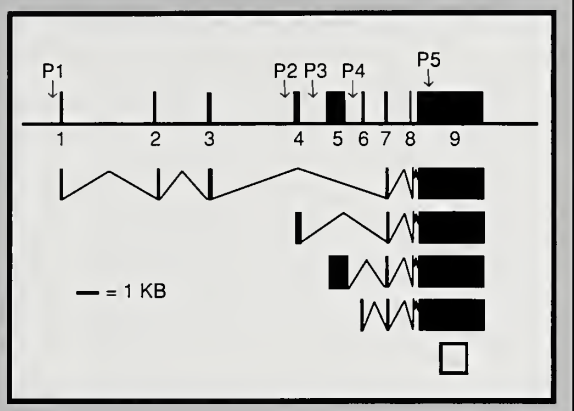
REGULATION OF INSULIN-LIKE GROWTH FACTOR EXPRESSION

In the embryo and fetus, the factors that regulate IGF expression are for the most part unknown. A number of findings indicate that the control of gene transcription is extraordinarily complex. IGF-1 and IGF-2 are each encoded by single large genes, spanning about 95 and 35 kb of human genomic DNA, respectively.[16,17] Each gene contains multiple exons, at least 6 for IGF-1 and 9 for IGF-2, some of which are used alternatively to generate transcripts of differing composition (see Figures 2 and 3). Genomic DNA 5′ to each of the first utilized exons includes multiple putative consensus regulatory sequences (nucleotide sequences that are known to bind transcription factors), but none of these flanking regions contains classic TATA promoters or known response elements. Thus, IGF transcription appears to be regulated by mechanisms that differ from those that have been classically defined. Because IGF transcripts differ in a fashion that depends on the cell

Figure 2
Human Insulin-Like Growth Factor 1 Gene and Transcripts

The human IGF-1 gene (top schematic) spans approximately 95 kb of genomic DNA on the long arm of chromosome 12. It contains at least 6 exons (black boxes) that are utilized to transcribe a number of mRNAs (lower 4 schematics). Exons 1 and 2 encode portions of alternative signal peptides. Because these exons may contain several transcription start sites, transcripts in addition to those depicted are likely transcribed. Exon 3 encodes the remaining signal peptide sequence and most of the β domain of mature IGF-1, while exon 4 encodes the remainder of mature IGF-1 and the amino-terminal end of the trailer peptides. Exons 5 and 6 encode the alternatively used segments of the trailer peptide. IGF-1 mRNAs vary dramatically in their length and most of this size difference is due to the length of 3′ untranslated RNA encoded on exons 5 and 6. These differences are not depicted.

Figure 3
Human Insulin-Like Growth Factor 2 Gene and Transcripts



The human IGF-2 gene (top schematic) lies immediately adjacent to the insulin gene on the short arm of chromosome 11 and spans approximately 35 kb of genomic DNA. It is composed of 9 exons (black boxes) that are alternatively used to generate multiple IGF-2 mRNAs. Exon 7 encodes the signal peptide and most of the domain of the mature protein. Exon 8 encodes the remainder of mature IGF-2 and the beginning of the trailer peptide, and exon 9 encodes the remainder of the trailer sequence. Exons 1 through 6 encode 5′ untranslated RNA. Putative promoters for IGF-2 are marked (P1-P4). The open box at the bottom represents an mRNA that does not encode IGF-2 and is presumptively regulated by sequences depicted as P5.

of expression and its developmental stage, it seems certain that distinct factors regulate their expression in different tissues. The finding in adult animals that estrogens stimulate the abundance of IGF-1 mRNA in uterus but not in liver, while growth hormone does the opposite, strongly supports this speculation. In several cultured cells derived from fetuses, placental lactogens stimulate IGF production, although the mechanism by which this is accomplished is not known.[18] Cultured fetal adrenal cells dramatically increase their abundance of IGF-2 mRNA after exposure to corticotropin. In vivo IGF-1 expression is reduced in experimentally induced fetal growth retardation; this may be mediated by impaired or inadequate nutrition, which has been shown to decrease fetal liver IGF-1 mRNA. No other specific substances, however, have been definitively implicated in the regulation of IGF expression in the embryo or fetus.

MECHANISMS OF INSULIN-LIKE GROWTH FACTOR ACTION

The IGFs initiate their actions by binding to cell surface receptors that transduce signals across the cell membrane.[19-22] Three, and

possibly 4, transmembrane proteins are capable of binding IGFs. It seems possible that the interaction of the IGFs with different receptors could result in altered responses to the IGFs and help explain the varied responses stimulated by the IGFs. Most of the known biologic actions of IGF-1 and IGF-2 have been associated with their interaction with the type 1 IGF receptor. It is heterotetrameric, with marked homology to the insulin receptor, and is composed of 2 heterologous pairs of disulfide bond-joined subunits. The α subunit is extracellular and binds the IGFs, as well as insulin (IGF-1 > IGF-2 > > insulin), while the β subunit spans the cell membrane and is phosphorylated rapidly following IGF binding. The autophosphorylation of the β subunit is thought to result in the phosphorylation of cytosol substrates, which in turn sets in motion a cascade of undefined events leading to biologic change. The type 1 IGF receptor is expressed from the 8-cell stage of embryogenesis and its mRNA is widely distributed in mid-gestation rat tissues.

IGFs also bind to the insulin receptor, but because the affinity of the insulin receptor for the IGFs is low, it is unlikely that this receptor interacts with physiologic concentrations of IGFs. Hybrid receptors composed of α and β subunits of both the type 1 IGF receptor and the insulin receptor have been shown to exist, and it is appealing to speculate that they may mediate specific IGF actions.[19] A gene for another possible receptor, termed the insulin receptor-related protein, has recently been cloned. It is equally homologous with type 1 IGF receptor and insulin receptors.[21] The structure of the insulin receptor-related protein gives it the potential to mediate IGF actions, but it is not known whether this protein is expressed in utero.

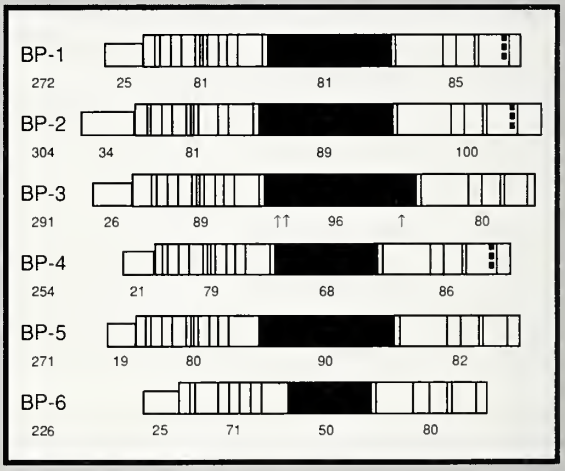
The type 2 IGF receptor is a single-chain protein that contains multiple repetitive sequences in its extracellular domain and is identical to the mannose-6-phosphate receptor. Interaction of IGFs and this receptor has not been convincingly linked to the growth-promoting actions of the IGFs, but its capacity to translocate enzymes, and possibly the IGFs, to lysosomes may be important in modulating IGF actions by initiating IGF degradation. The type 2 IGF receptor is expressed from the 2-cell stage and is abundant until late in rodent gestation. Its cellular distribution corresponds closely to that of IGF-2 mRNA, suggesting that its function is coupled to that of IGF-2.

MODULATION OF INSULIN-LIKE GROWTH FACTOR ACTION

An additional complexity to understanding the actions of IGFs is the finding that their actions are often exerted in concert with other agents. Studies of the mitogenic actions of IGF-1 using Balb c/3T3 cells show that these cells traverse the cell cycle only after exposure to IGF-1 and other growth factors, an observation later made in a number of other types of cultured cells. For example, in rat thyroid-derived FRTL5 cells, IGFs stimulate DNA synthesis only in concert with thyroid-stimulating hormone (TSH). Such a scenario may also be relevant to the differentiated actions of IGFs. For example, the stimulation by IGF-1 of progesterone synthesis in cultured granulosa cells is greatly augmented and becomes significant only when follicle-stimulating hormone (FSH) is present.

The actions of the IGFs also are modulated by specific IGFBPs.[6, 23, 24] Six distinct IGFBPs, each bearing a numerical designation, have been identified and their cDNA sequenced (see Figure 4). All the IGFBPs possess conserved sequences of amino acids and numerous

Figure 4
Precursors of Rat Insulin-Like Growth Factor-Binding Proteins



The IGFBPs are a family of proteins with shared structural characteristics, and are conserved among different species. They are synthesized with signal sequences (small blocks). Their mature forms (large blocks) are composed of 3 domains: cysteine-rich conserved amino- and carboxy-terminal domains and nonhomologous domains that lie in the middle of the molecule (black boxes). The thin vertical lines represent the positions of cysteines in amino- and carboxy-terminal portions of the mature proteins. The thick vertical broken lines at the carboxy-terminal ends of IGFBP-1, IGFBP-2, and IGFBP-4 show the location of amino acid sequences having the potential to bind to integrin receptors (Arg-Gly-Asp in IGFBP-1 and IGFBP-2, and Lys-Gly-Glu in IGFBP-4). The arrows below IGFBP-3 indicate potential sites of glycosylation. The numbers below each schematic indicate the number of amino acids in the precursor of the appropriate portion of the molecule.

cysteine residues in similar locations at both the amino- and carboxy-terminal ends. In most experimental situations, IGFBPs have been found to decrease IGF actions, presumably by binding IGFs and, thus, restricting their access to cell surface receptors. Such an inhibitory role is suggested by the increase in IGFBP-1 expression found in experimentally induced fetal growth retardation. Evidence of a role for IGFBPs in augmenting and/or facilitating IGF action, however, also exists. For example, IGFBP-1 and IGFBP-2 can cross rat endothelium and may, therefore, have a role in the delivery of IGFs to tissues. Binding of IGFBPs to the cell surface may be important to IGF actions by facilitating IGF-IGF receptor interactions. The capacity of IGFBP-1 and IGFBP-2 to bind to the cell may depend on the presence of Arg-Gly-Asp (RGD) amino acid sequences that interact with integrin-type receptors on the cell surface. IGFBP-3, also capable of enhancing IGF-1 activity, does not possess RGD sequences but may adhere to cell surfaces through glycosylated moieties. IGFBP-1 and IGFBP-2 are abundant in utero, being expressed in a variety of tissues from at least mid-gestation. Insulin decreases IGFBP-1 and IGFBP-2 expression, while their blood levels rise with fasting. Additional factors, including the IGFs, likely regulate these binding proteins in utero.

SUMMARY

The IGFs can be viewed as signals for a variety of growth and developmental events. The specific biologic events that the IGFs stimulate, however, are determined by the signaling mechanisms expressed by target cells and the influence of other agents on these target cells. In addition, these actions appear to be dramatically modulated by the actions of specific binding proteins. A better understanding of the role of IGFs in utero will come from elucidation of the precise mechanisms of IGF action in specific cells.

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Intrauterine Growth Restriction Revisited

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INTRODUCTION

Early gestation is characterized by rapid cell division and organ development. These early events occur swiftly, as illustrated by closure of the neural tube between 19 and 29 days of gestation and by development of the heart from the time of the first heart beat at 21 days of gestation to its differentiation as a 4-chambered pumping organ by 56 days. Major malformations that may have profound influences on subsequent fetal growth and development are already established by the end of the third month. The second trimester is, in large part, a period of growth and functional refinement of those organ systems that must be mature by the time of delivery. The brain undergoes the waves of neural migration and differentiation that will provide the basis for the neural integration and behaviors that are necessary for postnatal survival. In addition, there is both rapid growth and functional differentiation of organ systems such as the lung and gut. By the end of the second trimester the fetus is at the brink of potential survival, as witnessed by infants born at 25 to 26 weeks of gestation and weighing 500 to 600 g who populate our newborn intensive care units with increasing frequency. While survival of such extremely

low-birth-weight infants is possible, it is not a desirable alternative to sustained growth in the intrauterine milieu, which during the last trimester results in a large increase in fetal weight. During this last 3 months of gestation there is deposition of storage fuels such as fat and glycogen, and the fetus more than quadruples in size. It is during this period that the fetus is vulnerable to those genetic and environmental insults that can interfere with normal growth.

INFLUENCES ON FETAL GROWTH

While fetal growth ultimately is controlled by the genetic endowment, it is nonetheless influenced by diverse factors. Male infants weigh 150 to 200 g more than females at birth, but this confers no survival advantage since infant mortality is greater in males. Size at birth differs greatly between different racial and ethnic groups; for example, the mean birth weight of populations in New Guinea is 2,400 g as compared with 3,880 g in American Indian populations. These weight differences likely reflect variation in maternal size and nutrition as well as genetic factors in different populations.

During fetal development there are important interactions between nutritional state and hormonal and growth factor influences. Insulin, as one of the principal hormones influencing fetal somatic growth, regulates fetal lipogenic activity and has a permissive role in hepatic glycogen deposition and protein synthesis. Fetuses with insulin deficiency secondary to pancreatic agenesis or with a defective insulin receptor, as in the "leprechaun" syndrome, have marked intrauterine growth retardation (IUGR) with decreased adipose tissue and little weight gain during the last trimester of pregnancy. Conversely, fetal hyperinsulinism results in increased adiposity in human infants of diabetic mothers. Other classic hormones, including thyroxin, glucocorticosteroids, and sex hormones, have important influences on specific organ development and on functional and metabolic adaptation but have little influence on somatic growth. For example, thyroid hormones are important for central nervous system (CNS) and skeletal maturation, glucocorticoids modulate lung maturation, and androgens are critical for sex differentiation. Pituitary growth hormone (GH) itself is not of great importance in the regulation of fetal growth and does not influence size at birth. However, a GH-like molecule produced by the placenta, known as placental lactogen or chorionic somatomammotropin, may have a role in modulating fetal growth. In the ovine fetus, maternal malnutrition reduces the number of placental lactogen receptors in fetal liver. The growth-promoting role of placental lactogen in humans is uncertain, however, since pregnancies in which the gene for placental lactogen is missing result in infants of normal birth weight.

Peptide growth factors that influence fetal growth and maturation include the insulin-like growth factors (IGF-1 and IGF-2, which are discussed by D'Ercole in this issue). In the fetus, these are independent of GH regulation. IGF-1 influences terminal differentiation of a number of tissues, including brain astrocytes, neural outgrowth, and myogenesis. Moreover, even though the influences of IGF-1 appear to be local, serum concentrations of IGF-1 correlate with birth weight.[1] Both IGF-1 and IGF-2 are complexed to binding proteins that modulate their biologic activity. Growth retardation in fetal rats caused by maternal starvation has been associated with decreased expression of IGF-1 and IGF-2 and increased expression of binding proteins in the liver, suggesting that these factors have a role in regulating fetal growth.[2] Epidermal growth factor (EGF) and EGF-α, which may be its fetal form, influence growth and differentiation of epithelial cells, including those in lung and gut. Receptors for EGF are present throughout development and are present in increased numbers in placenta and lung in fetuses with growth restriction induced by uterine artery ligation, suggesting a role for EGF in fetal growth retardation.[3] Additional evidence for an EGF effect on somatic growth is the observation that exogenous EGF administered to rats less than 2 weeks of age decreases growth. This effect of EGF has been related to suppression of IGF-1 concentrations in growth-restricted fetuses.[4] It is likely that the changes in blood flow that characterize the hemodynamic response to fetal nutrient restriction are modulated by endocrine mechanisms. Stressed fetuses have increased circulating levels of arginine vasopressin, which may contribute to the decreased splanchnic blood flow and increased blood flow to the brain that is associated with "brain sparing." Vasoactive prostaglandins also are of likely importance in modulating blood flow to the fetus and the hemodynamic changes resulting in brain sparing.

Maternal constraint of fetal growth and fetal adaptations occur under conditions of decreased nutrient supply or when fetal growth is inappropriate for maternal size. The latter may involve changes in growth factor or hormonal signaling. Mice selected for high plasma IGF-1 concentrations not only were larger but also produced litters with heavier fetuses than mice selected for low IGF-1 concentrations.[5] Maternal constraints on fetal growth also are illustrated by the classic study of Walton and Hammond showing that foals born to shire horses bred with female Shetland ponies are small and, therefore, were appropriate for maternal size. IUGR also may be multigenerational. A large reduction in

Letter to the Editor

In the December 1991 issue of *GGH,* you cite on page 9 our abstract on the protective effect of GH on steroid damage to bone. Your comment was imprecise, in that the presentation was made by me and not Dr. Raphael Rappaport. I am also not aware of any award to this paper from the ESPE.

Sincerely,
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Response From the Editor

Dear Dr. Hochberg:

You have learned of the fallibility of editors. Dr. Rappaport also informed me of my fallibility. Please accept my apologies. Your excellent abstract and presentation should have won an award. In that I am correct.

With embarrassment,
Robert M. Blizzard, MD

maternal weight and newborn size was observed in a marginally nourished rat colony maintained for over 12 generations. More than 1 generation was required to correct the deficit in fetal growth after reinstitution of normal nutrition.[6] Women who themselves experienced IUGR have an increased risk for giving birth to either IUGR or preterm infants. This again emphasizes the importance of maternal factors and the intrauterine milieu.[7]

DEFINITION

IUGR, or more preferably, intrauterine growth restriction, represents a final common pathway by which genetic and environmental influences result in low birth weight for gestational age. IUGR has been defined most commonly in the United States as a birth weight of less than the 10th percentile for gestational age. This broad definition has resulted in confusion since it is unreasonable to consider 10% of all births as being characterized by pathologic restriction of growth. Small infants in whom there is no evidence that adverse genetic or environmental influences are limiting growth should be spared the IUGR label, which connotes pathology, and should be defined as small-for-gestational age (SGA). Further refinements of these definitions include the following: (1) "small-for-gestational age" should be applied to all infants <10th percentile; and (2) "intrauterine growth restriction" generally should be reserved for infants <3rd percentile, in recognition of the fact that some infants with growth restriction will fall out of this range if an insult occurs late in gestation. Thus, while all IUGR infants also will be SGA, not all SGA infants will be IUGR.

The confusion is amplified further by the significant differences in 10th percentile birth weights at each gestational age that have been used to define IUGR in different published studies. Differences in published standards of growth have likely been influenced by racial composition, socioeconomic status of the population studied, and elevation above sea level when the standards were developed. The commonly used Lubchenko grids, for example, were developed in Denver, which is approximately 5,000 feet above sea level; IUGR may be underestimated when these charts are used at sea level. What is necessary for an effective comparison between populations is the adoption of a single standard for fetal growth, for example, the standards developed by Brenner based on 30,772 deliveries made at 21 to 44 weeks of gestation in Cleveland.[9] These standards include correction factors for poverty, race, and sex.

CLINICAL PRESENTATION

Genetic disorders associated with malformations or aneuploid chromosomal defects such as trisomy 18, Down syndrome, or Turner syndrome are obvious causes of IUGR. Infants with decreased growth potential due to structural or genetic defects; congenital infections, including syphilis and HIV infection; and toxic exposures, eg, heroin, cocaine, or alcohol, have a pattern of growth characterized as proportional or symmetric IUGR. That is, head circumference, length, and weight show the same degree of growth restriction and fall within the same percentiles for gestational age. Most infants with this pattern of IUGR born after 36 weeks continue to exhibit sluggish postnatal growth. IUGR also can result from maternal malnutrition or decreased uteroplacental blood flow in maternal disease states such as hypertension and diabetes, in which there may be decreased substrate delivery to the fetus.

Fetuses with growth restriction due to nutritional compromise show greater variability in body proportions and tend to have sparing of head growth.[10] Other conditions in which fetal nutrition is compromised include multiple pregnancies and the smaller of twins in which arteriovenous communications in the chorionic plate limit blood flow to one twin. IUGR also is seen in infants born at high altitudes or to mothers with cyanotic congenital heart disease,

presumably because of decreased oxygen availability. The infants with so-called disproportional or asymmetric IUGR resulting from nutritional compromise can show rapid catch-up growth after birth, but approximately 30% of such infants are still below the 5th percentile at 2 years of age. Infants with disproportional IUGR may be at risk for hypoxic injury, hypoglycemia, hypothermia, and polycythemia due to a chronically hypoxic state. These infants, however, can also be viewed as undergoing an adaptation to an adverse intrauterine environment. For example, constrained fetal growth in the presence of decreased uteroplacental blood flow can be considered an adaptation that decreases oxygen and substrate requirements and contributes to fetal well-being. The sparing of head growth reduction exhibited by IUGR fetuses results from an apparent increase in blood flow to the brain via the carotids when umbilical flow is compromised. IUGR fetuses with head sparing exhibit decreased umbilical blood flow as determined by Doppler flow measurements, and increased carotid flow.[11] An increase in circulating red cell mass, which can increase oxygen transport to fetal tissues, is another adaptation in IUGR. Polycythemia sufficient to result in hyperviscosity at birth can, however, result in neurologic impairment. The IUGR fetus may exhibit functional adaptations to decreased nutrition, such as accelerated lung and neurologic maturation, that would enhance its likelihood of extrauterine survival if born early. Growth-restricted newborns can be neurologically accelerated by 3 to 4 weeks when compared with normal-growth newborns of the same gestational age.[12]

Strategies to treat fetal growth retardation include therapies to decrease the platelet aggregation and uteroplacental circulation abnormalities seen in toxemia of pregnancy. Other treatments have included maternal nutritional supplementation and oxygen therapy. In a promising study of 323 women at risk for fetal growth retardation, administration of 150 mg/d aspirin resulted in a 225-g newborn weight increase over the placebo group and a frequency of growth retardation only 50% of the placebo group.[13] The beneficial effect of low-dose aspirin likely relates to inhibition of the synthesis of thromboxane B_2, which decreases the platelet aggregation and placental vasocclusion seen in the toxemic state. Although some studies have suggested a benefit to maternal parenteral nutritional supplementation, the long-term results have not been convincing. An adverse influence was observed when short-term administration of glucose to normal patients before delivery resulted in a significant increase in lactic acid and a fall in pH.[14] Direct fetal nutritional supplementation via the amniotic fluid has been successfully carried out in the ovine fetus, but there is little experience in human pregnancy.[15] Philipps et al[16] reported that direct glucose infusion in the fetal sheep raised fetal metabolic rate and increased fetal oxygen consumption. It is likely that these responses would be exaggerated by intra-amniotic infusion of nutrients to fetuses in which there is already compromise of oxygen delivery. When the fetus is "adapted" to decreased nutrient supply, there may be potential risk to increasing nutritional intake without a corresponding increase in fetal oxygenation.

In Future Issues

Growth Hormone Deficient-Like Syndromes and Their Etiologies
by William H. Daughaday, MD

The Effect of Irradiation on Endocrine Function in Children: Past, Present, and Future
by Stephen M. Shalet, MD

Fragile X Syndrome: Current Status
by David Nelson, PhD

SUMMARY

Since this topic was presented in *GGH* 5 years ago,[17] we have witnessed an increased understanding of fetal growth influences, particularly the role of fetal growth factors, as well as improved methods of obstetric diagnosis and treatment of intrauterine growth restriction. However, epidemiologic research remains hampered by the lack of a broadly used standard for defining growth. In addition, there is an increasing recognition that some features of IUGR infants, such as low birth weight, polycythemia, and advanced maturation, are actually adaptations to an adverse uterine environment that may enhance fetal survival.

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Special Report

Eighth International Congress of Human Genetics
October 6-11, 1991, Washington, DC

Over 5,000 persons attended the Eighth International Congress of Human Genetics, making it by far the largest gathering of human geneticists ever. It is virtually impossible for any one person to provide a complete review of the congress since its size dictated simultaneous sessions for almost the entire meeting. Indeed, after a brief opening session, the congress broke up into 52 concurrent workshops, 16 concurrent symposia, 10 concurrent slide symposia, and 10 concurrent slide sessions, all of which extended over 5 days and covered every conceivable topic related to human genetics. As well, there were nearly 2,500 posters. Nevertheless, there were themes that surfaced recurrently and other items worthy of comment as outlined below.

Developmental genetics was a hot topic. There were a number of papers in which animal models of human disease were described. The use of mice carrying mutant transgenes or mice in whom endogenous genes had been disrupted by gene targeting has eliminated the need for spontaneously arising mutations and provided considerable new insight into early human development and how malformations arise. Imprinting received considerable attention. Although not well understood, the occurrence of imprinting in humans is now well accepted; and its contribution to causing disease was the subject of a symposium.

Genetic and physical mapping of the human genome is occurring at a rapid pace. The recent identification of several disease-associated genes was reviewed. Detection of mutations in the fibrillin gene in Marfan syndrome provides a good example. There was a time when excluding genetic linkage between a disease and a gene locus was considered negative information. However, such data are now being compiled to produce so-called exclusion maps (ie, identifying that part of the genome in which a particular gene locus does not reside) for many conditions. These continue to narrow down the chromosomal regions where disease-associated genes must reside and will eventually permit their localization.

There were many papers addressing the mapping of genes that predispose to common diseases, such as coronary artery disease and Alzheimer's disease, as well as rare diseases.

It has been known for many years that genes are regulated by transcription factors that bind to DNA in a highly specific fashion. Evidence has accumulated that large complexes composed of many proteins that bridge DNA binding sites are actually responsible for the control. It now appears that the fine-tuning of this control may depend more on the protein-protein interactions among the factors than on the protein-DNA interactions of the factors and the DNA binding sites.

Genetics is the study of variation and, as usual, many new syndromes and variants of established syndromes were described. However, in the case of the chondrodysplasias, a new and simpler nomenclature was unveiled. It groups the disorders into communities and families of chondrodysplasias that share common features and possibly common pathogenic mechanisms.

There was much interest in the technique of fluorescent in situ hybridization (FISH). The technique is being used to map genes to chromosomal sites and to determine the number of copies of particular genes or even chromosomes. For example, FISH was employed to detect chromosomal mosaicism in the placentas of infants with intrauterine growth retardation. The technique will probably see many new applications over the next few years.

A wide variety of new "things" were presented. They ranged from new ways to clone and map genes to new approaches for prenatal diagnosis, from new views on human evolution to better ways to set up disease registries and educate professionals and the laity about genetics. For most attendees, including myself, the congress provided many opportunities for information overload. Fortunately, most of the best new knowledge will appear or has recently appeared in the literature.

William A. Horton, MD

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Does Growth Hormone Treatment Improve Final Height Attainment of Children With Intrauterine Growth Retardation?

Results obtained with growth hormone (GH) treatment in 24 prepubertal (19 males, 5 females) intrauterine growth retarded (IUGR) children (ages 2 to 9 years; mean, 6.3 years) were reported. All patients' heights were less than the 3rd percentile. The mean growth velocity (GV) was -0.76 standard deviation (SD) for age. All had normal levels of GH during pharmacologic testing and/or overnight sampling. Eighteen were considered to have the morphologic features of Russell-Silver syndrome; 6 did not. Subcutaneous GH was given daily for 3 years at doses of either 15 IU/m²/wk (n=11) or 30 IU/m²/wk (n=13) the first year. All received 30 IU/m²/wk for the following 2 years. Puberty did not occur during the 3 years in any of the patients.

Mean GV (SD for age) increased during the first year to +1.4 with GH 15 IU/m²/wk and to +3.6 with GH 30 IU/m²/wk. It remained at +1.5 SD the second year and +1.1 the third year. There was great variability in individual results, with no differences between sexes or between the Russell-Silver patients and the others. However, there was no improvement of height SD score (SDS) for bone age. Therefore, the height prognosis did not increase (-1.6 SD at the onset of treatment and -1.5 at the end). Results were similar regardless of the dose received the first year.

The authors do not offer a clear-cut answer to the question asked in the article's title. They only note that there was no decrease in height for bone age, which usually occurs in IUGR children during the late prepubertal years. Thus, they postulate that these children could possibly reach a better final height than otherwise would have occurred. They also raise the idea that treatment may be of psychologic benefit because of the advanced tempo of growth.

Stanhope R, Preece MA, Hamill G. *Arch Dis Child* 1991;66:1180.

Editor's comment: *IUGR is a major cause of significant short stature, with a frequency approximating 1% of the total population. Although the positive short-term effect of GH in many children with abnormal birth lengths has been known for many years, the long-term effect on ultimate stature has not been known. The current study, which employed an excellent methodology, clearly shows that the value of GH in increasing ultimate height at least in Russell-Silver-associated short stature (and probably other types of IUGR) remains uncertain. The question is of great practical importance because of the handicap of severe short stature and the high cost of GH for treatment over many years. This study is not encouraging except in relation to increasing the tempo of growth, which can be important psychologically. Large-scale studies looking at ultimate growth, as well as tempo of growth, are taking place, and we must wait until these are completed to answer the question, "Does GH treatment improve final height attainment of children with IUGR?" Since this question will not be answered immediately, the routine or even frequent use of GH for IUGR patients cannot be encouraged on the basis of published data.*

J. C. Job, MD

Growth Status and Growth Rates of a Varied Sample of Low Birth Weight, Preterm Infants: A Longitudinal Cohort From Birth to Three Years of Age

The Infant Health and Development Program, a collaborative effort by 8 US medical schools, is the basis for this longitudinal study of the growth characteristics of low-birth-weight (LBW), *preterm* infants. In it, 985 LBW infants were grouped as follows:

Group	No.	Weight
1	149	<1,250 g
2	474	1,251-2,000 g
3	362	2,001-2,500 g

All infants were assessed at 40 weeks postconceptional age and at 4, 8, 12, 18, 24, 30, and 36 months, gestation-corrected age. Growth rates were estimated for 0 to 12, 12 to 24, and 24 to 36 months of age. Each measurement was available for at least 956 children.

Boys in each group differed significantly at all ages for length, weight, and head circumference. Girls differed significantly in head circumference at all visits, in weight until 24 months, and in length until 18 months. In summary, there was evidence of compensatory growth in length for both sexes in the first year of life but none thereafter. However, this is far from complete by age 36 months, gestation-corrected age. The data demonstrate that LBW preterm infants have different patterns of growth during the first years of life, as compared with term infants. Their growth should be monitored on grids developed from similar infants.

Casey P, Kraemer H, Bernbaum J, et al. *J Pediatr* 1991;119:599-605.

Editor's comment: *These data are the best yet available to compare the growth characteristics of LBW preterm infants with those of term infants. The data do differ from those of other investigators in that others have reported more "catch-up" growth than that reported here. However, as the authors point out, most other studies have been too small and/or have failed to maintain the cohort for long enough intervals to describe adequately the long-term status and patterns of growth in LBW infants. The authors, in total fairness, caution that these data include some on infants who were both preterm, which was a criterion for admission to the study, and LBW for gestational age. The authors plan to use these descriptive growth data to develop comparison standards for monitoring the growth of all LBW preterm infants independent of such clinical characteristics as size (appropriate-for-gestational age versus small-for-gestational age), presence of chronic neurologic disease, and the like. Current National Center for Health Statistics growth charts are not categorized by any such clinical characteristics. The authors are commended for diligently pursuing this complex problem and are encouraged to continue. Further data are very much needed, for example, to chronicle the differences in growth characteristics at all ages until adulthood is attained.*

W. L. Clarke, MD

Parental Imprinting and Fetal Growth

Insulin-like growth factor 2 (IGF-2) has long been implicated as an important fetal growth factor. Three recent reports now suggest that this effect is primarily due to expression of the paternally derived IGF-2 gene (called Igf2 to distinguish it from the gene product IGF-2).

DeChiara et al used gene targeting to disrupt Igf2 in embryonic stem cells that were employed to generate mice chimeric for the mutation. Once mice heterozygous for the mutation were established through breeding, transmission of the mutated gene was followed through several generations. The investigators found that when it was transmitted through the mother, there was no effect on the size of the offspring receiving the mutation. However, when transmitted through the father, the progeny receiving the nonfunctional Igf2 genes were growth-deficient and approximately 60% of normal size. Thus, among heterozygotes for the Igf2 mutation, only those receiving it from the father were growth-deficient. Using mRNA assays that distinguished between expression of the normal and mutated Igf2 genes, they further demonstrated that the maternal Igf2 allele was silent except in the choroid plexus and leptomeninges, where both alleles were expressed. They concluded that the maternal Igf2 allele is imprinted and therefore inactive in most tissues.

Beckwith-Wiedemann syndrome (BWS) is a fetal overgrowth syndrome in which tumors often arise. The constitutional karyotype is usually normal in the syndrome; however, in several instances DNA studies have demonstrated loss of the maternal contribution of genes that map to chromosome 11p15.5 in the tumors. This has been of considerable interest because it is the chromosomal site to which Igf2 maps in humans. Suspecting possible uniparental disomy for genes mapping to this region (both sets of genes come from 1 parent rather than 1 set from each parent), Henry and coworkers determined the parental source of several 11p15.5-mapped genes in 21 sporadic cases of BWS with normal karyotypes. The parental source could be determined for at least 1 gene in 8 instances. Three of these 8 had only paternal genes and therefore displayed paternal disomy.

The third report extends this story further. Igf2 maps to distal chromosome 7 in the mouse. Ferguson-Smith et al introduced cells from very early mouse embryos that carried duplications of either the paternal or maternal distal chromosome 7 into normal mouse blastocysts. The phenotype of the chimeric mice that were generated differed substantially depending upon the source of the 7p duplication. If the paternal duplication of distal 7 was present, the mice were substantially larger than control mice. In contrast, no size difference was noted when the maternal duplication for distal 7 was present. Comparison of mRNA levels for Igf2 showed increased Igf2 expression associated with the paternal distal 7 duplication but very low levels of Igf2 expression in the mice harboring the maternal distal 7 duplication.

DeChiara TM, Robertson EJ, Efstratiadis A. Parental imprinting of the mouse insulin-like growth factor II gene. *Cell* 1991;64:849-859.

Henry I, Bonaiti-Pellie C, Chehensse V, et al. Uniparental paternal disomy in a genetic cancer-predisposing syndrome. *Nature* 1991;351:665-667.

Ferguson-Smith AC, Cattanach BM, Barton SC, et al. Embryological and molecular investigations of parental imprinting on mouse chromosome 7. *Nature* 1991;351:667-670.

Editor's comment: *It is often held that maternal factors contribute more to fetal size than do paternal ones if for no other reason than that the fetus resides in the mother and is exposed to a host of maternally determined physical and chemical factors. However, these 3 investigations, utilizing completely different methods, strongly support the view that at least certain aspects of fetal growth are influenced more by the father than by the mother. The active Igf2 gene appears to be the one inherited from the father, whereas the maternally derived Igf2 gene is inactive in most tissues due to imprinting.*

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Prevention of Fetal Growth Retardation (FGR) With Low-Dose Aspirin

The efficacy of low dose aspirin therapy in preventing fetal growth retardation (FGR) was tested in a randomized, placebo-controlled, double-blind trial. The possible beneficial effect of adding dipyrimadole to aspirin also was tested. Studied were 323 women (29 to 45 years of age) who had been amenorrheic because of conception for 15 to 18 weeks. All had experienced at least 1 previous pregnancy with FGR and/or fetal death or abruptio placentae. They were randomized into 3 groups, receiving in double-blind fashion either:

Group 1 (n = 128) aspirin, 150 mg/d

Group 2 (n = 212) aspirin, 150 mg/d + dipyrimadole, 225 mg/d

Group 3 (n = 74) placebo

Twin pregnancies, uterine malformations, and histories of specific known previous disorders that could affect pregnancy outcome were reasons for exclusion from the study. Of the 323 subjects, 284 satisfied all the criteria and were considered eligible for the epidemiologic analyses.

The birth weight was significantly (P=0.029) better in the treated groups (2,759 ± 670 g) than in the placebo group (2,526 ± 848 g). The frequency of FGR, evaluated according to Lubchenco's percentiles, was 13% in the treated groups vs 26% in the placebo group (P=0.02). The incidence of stillbirths (5% vs 1%) and abruptio placentae (8% vs 5%) was more frequent in the placebo group. The mean duration of pregnancy reached 264 ± 19 days in the treated vs 258 ± 27 days in the untreated women (P=0.05).

The frequency of hypertension, proteinuria, hyperuricemia, and thrombocytopenia was similar in all groups. Apart from headache, which occurred in both the placebo and the treatment groups, the incidence of maternal side effects was very low, and no neonatal side effects were observed. In all these respects, no significant differences were found between the group receiving aspirin alone and that receiving aspirin plus dipyridamole.

The authors conclude that their study confirms the efficacy of low-dose aspirin given early in pregnancy in preventing FGR. They suggest that it acts on prostaglandins, and probably inhibits thromboxane production. They do not yet recommend widespread use of aspirin in pregnant women, since they are conscious that much larger scale trials are needed to determine its complete safety. Their conclusion is that low-dose aspirin treatment may be beneficial for any pregnancy considered at high risk of FGR, and they hope that early, reliable, and inexpensive markers of this risk will be found.

Uzan S, Beaufils M, Breart G, et al. *Lancet* 1991;337:1427-1431.

Editor's comment: *FGR, with its many immediate dangers for the child, is a major concern for neonatologists and obstetricians. It is also of extreme importance for all those who are interested in children's growth, since short stature of intrauterine onset appears to be the main type of severe height insufficiency (with a poor prognosis for adult stature) seen in pediatric and adolescent endocrine clinics. Thus, any attempt to reduce the frequency or degree of FGR may have a great impact on improving this pediatric situation. Although it is on the obstetrical side of fetal medicine, this trial should be of direct interest for all growth specialists.*

J. C. Job, MD

Developmental Genes and Birth Defects

Although mutations of genes involved in early embryologic development have long been suspected as causing birth defects in humans, direct evidence has been lacking. The "suspect" genes are those involved in determining the basic body plant of the embryo. Their products typically regulate expression of other genes and provide position signals that help to control developmental patterns. Several classes of genes have been characterized in lower organisms, particularly in *Drosophila*, based primarily on the patterns of malformation produced when mutations occur. Comparable genes are now being identified in higher organisms, including humans. The 2 papers described below implicate mutations of these genes in 2 human malformation syndromes.

The Greig cephalopolysyndactyly syndrome (GCPS) is an autosomal dominant condition characterized by macrocephaly, unusual facies, and polysyndactyly of the hands and feet. Previous cytogenetic studies in families exhibiting translocations had localized the mutation site to chromosome 7p13. To identify the gene(s) involved Vortkamp et al produced a panel of human-mouse hybrid somatic cell lines from 3 different GCPS patients in whom a chromosomal translocation had produced a small deletion of chromosome 7p. These cell lines contained human chromosome 7 material that bordered the translocation breakpoints both proximally and distally, thus allowing analysis of the deleted or disrupted genes. Hybridization of probes to different portions of a gene called *GL13*, which was recently mapped to this chromosomal region, showed that in 2 cases the translocation breakpoint disrupted the *GL13* gene in the first third of the molecule. Such a mutation would be expected to truncate the *GL13* protein. The third translocation localized outside the coding region of the gene and was thought to have caused its adverse effect by reducing expression of the adjacent *GL13* gene. The authors concluded that all 3 translocations led to reduction in the formation of functional *GL13* protein. Pertinent to this discussion, *GL13* encodes a so-called "zinc finger" DNA-binding protein that is thought to be a member of the *GLI*-Kruppel gene family. In lower organisms these genes play crucial roles in early development, and mutations thereof produce position-specific malformations.

In a second paper, Chisaka and Capecchi employed the technique of gene targeting to generate mice in which the homeobox gene *Hox-1.5* was disrupted. The *Hox* gene products are transcription factors that regulate development within specific segments of the developing embryo; *Hox-1.5* is expressed roughly in the region corresponding to the branchial arches. They disrupted the gene in pluripotential embryonic stem cells, introduced colonies of cells carrying the disrupted gene into early mouse embryos to generate mice chimeric for the disrupted gene, and then bred the mice to produce offspring heterozygous or homozygous for the mutant *Hox-1.5* gene. The heterozygotes for the mutation were normal. However, the homozygotes died at or shortly after birth and exhibited malformations involving the thymus; parathyroid and thyroid glands; and structures of the throat, heart, arteries, and cranium and facies. This pattern of malformations was remarkably similar to that observed in the DiGeorge syndrome, and the

authors proposed this mouse be used as an experimental model to study the human syndrome. The mechanisms by which such a mutation could produce the observed malformations was discussed at length in the article and in an accompanying editorial by Wright and Hogan.

Vortkamp A, Gessler M, Grzeschik K-H. *GL13* zinc-finger gene interrupted by translocations in Greig syndrome families. *Nature* 1991;352:539-541.

Chisaka O, Capecchi MR. Regionally restricted developmental defects resulting from targeted disruption of the mouse homeobox gene *Hox-1.5*. *Nature* 1991;350:473-479.

Wright C, Hogan B. Another hit for gene targeting. *Nature* 1991;350:458-459.

Editor's comment: *It must be emphasized that the brief descriptions above grossly oversimplify how genes control early embryologic development as well as the nature and interpretation of the experiments reported. Nevertheless, they serve to illustrate that the field of molecular developmental biology is rapidly moving from flies, frogs, and mice to humans, and is finding direct application to the understanding of human developmental abnormalities, ie, birth defects. As pointed out by Wright and Hogan, many other genes involved in early development are currently being studied by gene targeting and related approaches. The results of these investigations should provide a wealth of new information about the causation of human birth defects in the near future.*

William A. Horton, MD

Activating Mutations of the Stimulatory G Protein in the McCune-Albright Syndrome

The cause of the clinical symptomatology in McCune-Albright syndrome (MAS), including sexual precocity, multiple hyperfunctional endocrinopathies, polyostotic fibrous dysplasia, and café au lait spots, has been the subject of extensive speculation for many years. The capability of modern genetics to examine mutations of genes has now made it possible to specifically identify an abnormal mutation within exon 8 of the G protein α-subunit (Gsα) that stimulates cyclic adenosine monophosphate (cAMP) formation. Four patients with severe MAS were studied by the authors and identified as having a mutation of the Arg^{201} position in tissue. Two of the 4 had an His mutation and the other 2 a Cys mutation. The abundance of mutations in different tissues was variable. Not only was there evidence determined for mutations in testis, ovary, adrenal, pituitary and thyroid but also in the heart, lung, liver, kidney, thymus, and spleen. Two of the 4 patients died a sudden death, which may have been related to cardiac dysfunction. Unfortunately, the authors were unable to determine whether mutations were present in the polyostotic lesions or in the café au lait hyperpigmentation. Reasonable explanations are given why the mutant was not demonstrable in these 2 tissues as studied. In an editorial in the same issue, Dr. Michael Levine of Johns Hopkins reports finding the same defect in affected skin of 1 patient. Therefore, the defect remains to be identified only in bone, and this will probably be demonstrated in the near future.

The mutant abnormality produces a significant decrease in the guanosine triphosphatase (GTPase) activity of the α-subunit of the G protein, with the end result of increased adenylyl cyclase activity.

The authors appropriately state that for each case only 1 specific mutation (R201C or R201H) is detected, which is consistent with a monoclonal abnormal cell population. This mutational event occurs prior to development of the trilaminar disc because of the widespread distribution and mutation of tissues derived from all 3 embryologic germ layers, and because of the variable abundance among tissues within a given patient. The absence of mutation in at least 1 tissue from each case is consistent with a somatic rather than germ line mutation. Intriguingly, the Gsα mutations were present in virtually all affected MAS endocrine tissues analyzed. The affected tissues within each organ had a greater proportion of the mutant population than did the unaffected tissues. The presence of activating Arg^{201} mutations was first described in sporadic growth hormone-secreting pituitary adenomas, which have autonomous cAMP synthesis. Importantly, the authors clarify the association between Albright's hereditary osteodystrophy (AHO) and MAS. AHO is associated with Gsα gene mutations, which lead to a deficiency in G protein. The mutations within MAS are different but of the same gene. Mutations in AHO impair the G protein signal transduction pathway while those found in MAS have the reverse effect, ie, the activation of the G protein pathway, an effect that probably underlies the clinical manifestations of the syndrome.

Weinstein LS, Shenker A, Gejman PV, et al. *N Engl J Med* 1991;325:1688-1695.

Editor's comment: *The findings reported in this article are exciting, thoroughly done, and now give us a much better understanding of MAS phenomena. The authors are to be congratulated for their fine work and for their contribution.*

Clinicians now must be made aware that the symptomatology in severe cases of MAS may be much greater than previously understood. The presence of the mutant gene in multiple tissues can lead to diverse clinical pathophysiology. Incomplete presentations of MAS may represent cases in which there is an even more limited distribution of mutant cells. Liver, cardiac, and renal disease need to be considered in patients who present with MAS. Undoubtedly a much larger group of these patients than previously demonstrated produce excessive growth hormone, which may account for the fact that many patients with MAS do not have the short stature we usually expect in the typical patient with sexual precocity. Unexplained as yet is the significantly higher incidence of this syndrome in females than males.

Those interested in this report also will want to read the editorial by Dr. Michael Levine in the same issue of the New England Journal of Medicine, *entitled "The McCune-Albright Syndrome: The Whys and Wherefores of Abnormal Signal Transduction."*

Robert M. Blizzard, MD

Standardized Percentile Curves of Body-Mass Index for Children and Adolescents

The data collected in the First National Health and Nutrition Examination Survey (NHANES I) from 1971 to 1974 were used to construct centile curves for body-mass index (BMI, kg/m^2) for white US boys and girls (ages 1 to 19 years). The raw means for each age were smoothed by quadratics fitted in 2 sections (males, 1 to 11 years and 8 to 19 years; females, 1 to 13 years and 6 to 19 years) and by splicing the 2 sections together (males at 10 years and females at 7 years).

The curves for BMI, by percentiles, for males and females are reproduced in Figure 1. Percentile values in tabular form are presented in the article, and these values will be of importance to those investigators concerned with relating BMI to other growth characteristics.

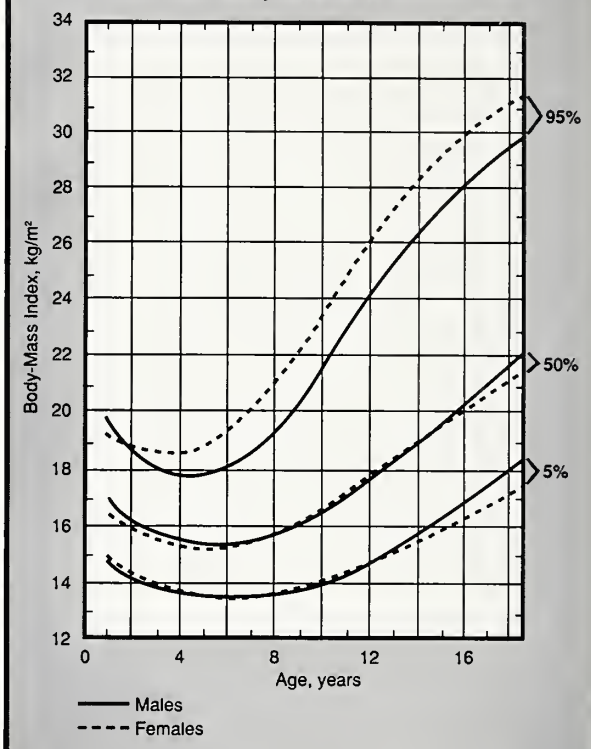
The authors conclude that these curves may be used to monitor the development of obesity as well as changes in BMI associated with treatment of obesity in childhood and adolescence. The pattern of BMI has been shown to be a predictor of long-term obesity in childhood and to predict morbidity and mortality in adulthood. Therefore, it is recommended that clinicians routinely measure height and weight and monitor BMI in children and adolescents. BMI curves should be developed for other racial groups as well. Further studies also are needed to define appropriate BMI cutoff points to more precisely define obesity in childhood and adolescence.

Hammer LD, Kraemer HC, Wilson DM, et al. *AJDC* 1991;145:259-263.

Editor's comment: *These curves provide useful cross-sectional standards for BMI for white US children. Admittedly, they relate to the 1970s and values today may be somewhat higher. The NHANES survey oversampled lower socioeconomic groups, but within-age analysis of the data did not show any significant socioeconomic differences. Thus, no adjustment for socioeconomic level was made. These are probably the best childhood population standards for BMI to date.*

James M. Tanner, MD

Figure 1
Body-Mass Index



Body-mass index for white males and females aged 1 to 19 years. Percentiles were computed using data from the First National Health and Nutrition Examination Survey, 1971 to 1974.

Effect of Growth Hormone and Resistance Exercise on Muscle Growth in Young Men

Growth hormone (GH) treatment in childhood increases net body protein. GH in adults reportedly increases fat-free mass (FFM). Whether the increase in FFM is due to an increase in muscle protein is unknown. Fiber size of skeletal muscle, whole muscle area, and muscle force-generating capability increase with heavy resistance exercise training (HRET). However, it is unclear how human skeletal muscle and whole body protein turnover are affected by HRET. The purpose of this double-blind, placebo-controlled study was to determine the effects of HRET on FFM, muscle size and strength, the rate of whole body protein turnover, and the rate of protein synthesis in the quadriceps muscle, and to examine whether GH supplementation enhances the anabolic response to HRET.

Sixteen subjects completed a 12-week study in which all underwent a HRET program. Seven received approximately 40 µg/kg/d of GH and 9 received placebo. Appropriate and eloquent studies of body composition were carried out to permit answering of the questions asked. As determined by hydrodensitometry, FFM increased significantly in both groups, but the increment was greater in the GH-treated group. Since FFM is principally water, total body water increased in proportion to FFM in the 2 groups. Chest and upper arm circumference increased in both groups, but thigh and mid-thigh circumference increased only in the GH-treated group. Muscle strength improved identically in both groups, as did increments in concentric force production. Whole body protein synthesis increased more in the GH-treated group, as did body protein balance.

The authors concluded that HRET increased FFM, muscle size, and muscle strength, and tended to increase the fractional rate of quadriceps muscle protein synthesis. GH treatment added to the training regimen (HRET) produced no significant further increase in muscle size, muscle strength, or fractional rate of muscle protein synthesis. The results indicate that pharmacologic doses of GH given to young men with normal GH secretory function do not enhance skeletal muscle protein accretion or muscle function more than resistance training without GH treatment. The greater increase in FFM and whole body protein synthesis rate observed in the GH-treated group indicates that these individuals accumulate additional lean tissue, but it is unlikely that this tissue was skeletal muscle protein. Therefore, the rationale for using GH to amplify exercise-induced muscle growth and thus enhance athletic performance appears to have no foundation in fact.

Yarasheski KE, Campbell JA, Smith K, et al. *Am J Physiol.* 1992;25:261-267.

Editor's comment: *Amen. A precise, lucid study that all aspiring potentially muscle-bound athletes should read.*

Robert M. Blizzard, MD

Treatment of Children With Down Syndrome and Growth Retardation With Recombinant Human Growth Hormone

Short stature is known to be one of the features of Down syndrome (DS). The authors treated 13 children with DS who were short for age (standard deviation score [SDS] -1.19 to -3.5), microcephalic (-1.58 to 6.60 SDS), and had no heart disease. Before treatment, peak serum growth hormone (GH) concentrations were less than 10 µg/L after levodopa and clonidine stimulation tests in 5 patients, after clonidine in 3 patients, and after levodopa in 3 patients. Three patients had nocturnal integrated GH concentrations of 0.5, 1.5, and 0.65 µg/L, respectively. The endocrine findings before treatment were normal with respect to luteinizing hormone, follicle-stimulating hormone, estrogen, testosterone, prolactin, thyroid-stimulating hormone (TSH), thyroxine, and triiodothyronine.

The patients were given recombinant human GH (rhGH), 0.1 mg/kg subcutaneously, 3 days a week for 1 year. The mean growth rate before treatment was 5.4 ± 1.6 cm/yr and increased to 12.2 ± 3.2 cm/yr ($P<0.001$) after 12 months of rhGH treatment. The mean head circumference SDS before treatment was -3.1 ± 1.3 and increased to -2.3 ± 1.2 ($P<0.001$) at 12 months.

Two patients in whom elevated serum TSH concentrations developed while on rhGH treatment for 6 months were started on levothyroxine treatment. Bone age increment during the year of treatment corresponded to the increment in chronologic age. Plasma hemoglobin A_{1c} concentration remained normal. The mean plasma concentrations of insulin-like growth factor 1 at baseline and at 12 months were 0.54 ± 0.19 U/mL and 1.25 ± 0.97 U/mL, respectively ($P<0.02$). The authors concluded that rhGH therapy can result in a significant increase in annual growth rate and head circumference in children with DS, without significant side effects.

Torrado C, Bastian W, Wisniewski, et al. *J Pediatr* 1991;119:478-483.

Editor's comment: *This provocative paper offers rhGH as a treatment for short stature and microcephaly in children with DS. The most impressive part of the study is the remarkable response of DS patients to GH treatment. They exhibited catch-up growth with a mean of 12.2 ± 3.2 cm/yr, which is impressive even for patients with hypopituitarism. However, we have to point out several pitfalls of this study, including the lack of data to ascertain the possible causes of GH alterations in DS.*

First of all, the height and weight of the patients were compared with growth charts for normal children rather than the standards for children with DS. The growth pattern of these patients should be compared with children who have the same chromosomal defect.[1] *No details were given about the age, sex, and pubertal stage of the patients.*

Second, the authors come to the conclusion that neurosecretory problems were the cause of growth retardation. However, only 3 patients had integrated GH studies showing decreased GH levels. The criteria for neurosecretory dysfunction of GH in otherwise normal children are being debated.[2] *In patients with problems such as DS, there would be much more debate to establish the criteria for this diagnosis. These patients did not meet the classic criteria of neurosecretory GH dysfunction. The growth velocity before treatment was above normal (5.4 cm/yr) instead of the usual decreased growth rate (below 4 cm/yr). Only 2 of the 13 patients had normal secretion of GH with pharmacologic provocative tests, which differs from the classic criteria and implies a normal response to pharmacologic stimulus and decreased physiologic levels. However, further explanations need to be sought for the excellent response to GH therapy. If this response was not associated with puberty or other factors in medical care that improve growth, it might suggest that DS patients present with a form of GH resistance as seen in other conditions, ie, uremia.*

There might be another explanation for the GH unresponsiveness to pharmacologic stimulus. The body weights of these patients were not reported. Nonetheless, the SDS for weight (-1.0 ± 0.7) was higher than the SDS for height (-2.2 ± 0.8). It is a well-known fact that obesity is associated with decreased GH responsiveness.

This paper, despite its deficits, does imply that further double-blind, placebo-controlled studies should be undertaken to clarify the pathogenesis of growth retardation and to confirm the response to rhGH treatment in DS. Moreover, changes in head circumference and its correlation with intelligence must be studied in more detail. Caution should be exercised in initiating GH treatment in DS patients, unless it is undertaken as part of a carefully controlled and well-designed scientific study.

Fima Lifshitz, MD

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Volume 7, Number 1

Abstracts:

Volume 7, Number 2

Abstracts:

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ACCESS TO TREATMENT WITH HUMAN GROWTH HORMONE:

Medical, Ethical, and Social Issues

A Special Proceedings Supplement

Dear Colleague:

You as a reader have an exciting opportunity. These presentations and discussions of a symposium that was entitled, "Access To Treatment With Human Growth Hormone: *Medical, Ethical and Social Issues,*" represent possibly your first opportunity to learn and evaluate how ethicists, philosophers, and economists regard the endeavors of pediatricians to assist very short children to grow.

This conference, held October 27 and 28, 1991, was limited in attendance to a few pediatric endocrinologists and ethicists because of expenses. You who were not present may be at an advantage. Why, you might say? My reply is based on my personal wish to have been present and involved. I thought being absent would hinder my learning what individuals in different disciplines thought about growth hormone (GH) therapy. Given subsequent conversations with the attendees that identified their significant frustrations at having their secure concepts regarding treatment of growth hormone deficient (GHD) or GHD-like short children questioned, these transcripts were received with some anxiety. There was no need for that. Reading the transcripts exhilarated me because there was so much to learn about the attitudes and concepts of ethicists from the fields of philosophy, economics, and religion.

My absence from the conference spared me the anxiety and frustration of becoming emotionally involved. You also have been spared these initial frustrations and anxieties. Reading the transcripts opened entire new areas of thoughts and information for me to ponder. You, hopefully, will have the same experience.

An editor has multiple responsibilities. One is to assist the reader to gain the maximum return or rewards for the time invested. Because these proceedings are lengthy, and undoubtedly your time is limited, I would like to suggest an approach that may give you the maximum return for your invested time.

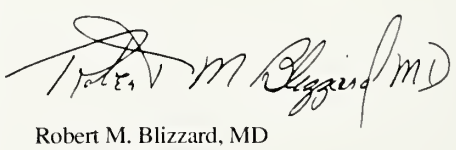
Immediately after reading this introduction, scan the "Table Of Contents," the "Presentation Content Outline," and the "List Of Participants" for identification of their qualifications to participate. After reviewing the outline, you may have priorities for further reading. Hopefully, you will decide to invest adequate time to read the proceedings completely. However, you may not have that luxury. Regardless of how much of the contents you intend to read, first read the introduction and preface to each of the 5 sessions by Dr. David Allen which will give you insight into the goals of each session. Then, I suggest that you read the summation papers in Session V by Drs. Lantos and Allen. I believe practicing pediatric endocrinologists may prefer to then read the presentations and discussions in Session III, "Conceptual and Ethical Issues in Entitlement to GH Treatment," and/or Session IV, "Socioeconomic Issues Relevant to the Treatment of Short Stature." Fellows in pediatric endocrine training, pediatricians, and pediatric residents may wish to focus first on Session I, "Determining GH Insufficiency and the Efficacy and Toxicity of Human GH Therapy" and/or Session II, "Psychologic and Social Issues in GH Therapy." I predict geneticists will not settle for less than reading it all. Nurses will select preferentially on the basis of their own interests and experiences. Ethicists will particularly enjoy Session II, "Psychologic and Social Issues in GH Therapy." All should complete their review by reading the "Concluding Comments" in Session VI by Dr. Alan Weisbard, whose remarks included:

> "In contrast to most conferences I attend, at this one I actually learned something. The most fascinating aspect of the conference has been the challenge of communicating across disciplinary divides....As I understand Dr. Stabler, whatever criteria one uses to distinguish GHD from non-GHD, height is not the only issue."

Incidentally, there is a recurrent paradigm that appears in the text that you may find confusing without further explanation. There is a reference to Johnny and Billy – 2 hypothetical patients with short stature – one who has growth hormone deficiency and one who does not. For more information, please see page 46 under the header, "Challenges to the Treatment/Enhancement Distinction."

Before encouraging you to turn to the outline and the participants list, please join me in recognizing and thanking the conference sponsor, the University of Wisconsin School of Medicine, Department of Pediatrics, and the commercial companies and foundations that provided funding for this educational event. These include Genentech, Inc., Eli Lilly, Inc., Ross Laboratories, the Turner Syndrome Society, the Human Growth Foundation, and MAGIC Foundation. Expressions of gratitude and appreciation also are due to Drs. David Allen and Norman Fost, who conceived, organized, and hosted this seminar. They have again proved themselves leaders in their fields.

On behalf of the Editorial Board of *GGH*,



Robert M. Blizzard, MD
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ACCESS TO TREATMENT WITH HUMAN GROWTH HORMONE:

Medical, Ethical, And Social Issues

Sponsored by:
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Madison, Wisconsin

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TABLE OF CONTENTS

PRESENTATION CONTENT OUTLINE

INTRODUCTION

Dear Colleague:

Widespread availability of human growth hormone (GH), along with advancing knowledge about its efficacy, are timely and important topics. Ten years ago, pituitary-derived GH was precious, and its rationing a necessity. The advent of recombinant DNA technology has made human GH abundant—abundant, but still expensive. Short children previously denied access to GH theoretically may now be treated. However, for many pediatric endocrinologists, this "feast" of GH has become more frustrating than its "famine." The luxury of availability has brought uncertainty, controversy, and discomfort to practitioners trying to do the *right thing* with GH. While we have learned much about GH in the past decade, we seem to know less about how best to use it.

One reason for this is that GH therapy has expanded beyond the boundaries of traditional endocrinologic endeavors, where missing hormones are replaced and excessive hormone production suppressed. GH availability has led to the development of GH *augmentation* therapy in addition to GH *replacement* therapy. And future goals of GH therapy appear likely to shift further toward supplementing and "enhancing" individuals' well-being rather than merely returning them to some physiologic baseline.

"Is it really GH deficiency?" was the perplexing question of the 1980s. Likely to dominate the 1990s, however, is debate among patients, parents, insurance companies, and physician colleagues about "How short is too short?" or " How tall is tall enough?" These are not medical questions; they are philosophic, psychologic, and economic questions. Continuing to do what we endocrinologists do best (eg, finding a better description of GH deficiency [GHD] or exploring new candidates for GH therapy) will not answer them. Today, only endocrinologists should prescribe GH. But in the future, endocrinologists alone will not be able to determine who is and is not entitled to it, especially if GH is effective for non-GHD children.

As a first step in this multidisciplinary process, we have convened physicians, medical ethicists, medical economists, and psychologists to explore ideas and concepts that may help to guide allocation of human GH. To facilitate discussion, several presenters have been asked to support extreme viewpoints that may not accurately reflect their own beliefs or practice. The current expense of GH obviously invites debate about allocation of health-care resources for the treatment of short stature from any cause. Subjecting children to long-term, invasive treatment requires evaluation of psychologic benefit and harm as well as potential toxicity. Augmenting height potential, perhaps at the expense of others who must do without GH, requires consideration of fairness and justice. The expertise of those who study and write about these aspects of health care will help to clarify these issues.

To those of us who *practice* health care and treat children with short stature, however, entitlement to GH is not an abstract issue. It is hoped that our discussions will also capture the emotional and ethical dilemmas arising from our sincere desire to do the best for every "real life" child, and our uncertainty whether what *can* be done with GH is, in fact, what *should* be done.

The success of this conference depends on an uninhibited, critical, and challenging sharing of ideas. To maintain a small group atmosphere, conference attendance had to be limited. Consequently, many outstanding and deserving individuals have been excluded, and to them I sincerely apologize.

I would like to acknowledge the extremely generous contributions from Genentech, Inc., which are largely underwriting both this conference and the proceedings publication. A great deal of credit is due them for their willingness to support an independent multidisciplinary examination of this issue. Additional support from Eli Lilly, Inc., Ross Laboratories, the Human Growth Foundation, the MAGIC Foundation, and the Turner Syndrome Society is also acknowledged and appreciated.

David B. Allen, MD
Editor-in-Chief

Session I:

DETERMINING GROWTH HORMONE INSUFFICIENCY AND THE EFFICACY AND TOXICITY OF HUMAN GROWTH HORMONE THERAPY

Editor's comments: My colleague and co-organizer Norm Fost always says that good ethics begin with good facts. Our first session explores current and emerging information about issues that are critical to the analysis of responsible use of growth hormone (GH): (1) the determination of GH deficiency (GHD), (2) the effectiveness of GH in the treatment of non-GHD short stature, and (3) the possible toxicity of GH therapy. The reader will undoubtedly note that, although our knowledge of GH therapy has advanced greatly in the last decade, *unified interpretations* of the facts we do have regarding definitions of deficiency and assessments of efficacy remain elusive.

David B. Allen, MD

METHODS OF ASSESSING GROWTH HORMONE SECRETION AND DETERMINING GROWTH HORMONE DEFICIENCY

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Introduction

The classic form of hyposomatotropism is a well-characterized clinical disorder due to genetic, structural, congenital, and acquired abnormalities of the hypothalamus and adenohypophysis. It is characterized by:

1. Subnormal secretion of growth hormone (GH) in response to 2 or more standard provocative stimuli in the clinically appropriate patient with:
   - Marked growth retardation,
   - Decreased growth velocity,
   - Delayed skeletal maturation,
2. Known insult (birth or head injury, cranial irradiation, intracranial surgery),
3. An anatomically defined lesion of the hypothalamus, pituitary stalk, or anterior pituitary,
4. An abnormality in the genetic structure of GH or GH-releasing hormone (GHRH), and/or
5. Absence of other explanations for growth retardation.

These criteria distinguish the truly GH-deficient (GHD) child from the child with partial deficiency of GH secretion who may be first evaluated during the evolution of classic hyposomatotropism when stimulated GH secretion is still normal, or who may have sufficient mass of somatotropes to respond to provocative stimulation but who does not release adequate GH on a daily basis to permit normal growth.

This paper will discuss methods of assessing GH secretion and action that help to define GHD. Initially, however, it is important to recognize that the diagnosis of subnormal secretion of GH is *not* the same problem as the selection of the child for GH therapy. These are 2 complementary, but distinct, challenges.

Measurement of Growth Hormone

Variability in the quantitation of GH levels continues to complicate the definition of deficiency. GH is most often measured by competitive immunologic and receptor binding methods, although bioassays for its determination also have been developed. In serum, GH is present as 22-kd and 20-kd species and in several isoforms that differ in size, charge, and immunogenicity.[1] GH circulates bound to high-affinity and low-affinity binding proteins; the high-affinity binding protein is identical to the extracellular domain of the plasma membrane receptor for GH.[2]

The heterogeneity of circulating GH has resulted in the development of immunoassays with differing specificities and sensitivities. Individual conventional first-generation radioimmunoassays (RIAs) employing polyclonal antibodies to GH often record discrepant GH values for the specimen because each antibody recognizes different epitopes or isoforms of somatotropin.[3,4] With the development of second-generation immunoradiometric assays (IRMAs) employing dual polyclonal and monoclonal antibodies, the specificity and analytic sensitivity of the assays improved, but discrepancies between various assays persisted. GH values as determined by RIA have been reported to be 1.5- to 2.0-fold greater than those determined by IRMA.[4,5] Enzyme-linked immunosorbent assays (ELISAs) and immunofluorescent assays (IFAs) for GH have increased assay sensitivity but the differences between assays remain.[6] Thus, interassay variability in measurements of immunologic GH concentrations is due to the heterogeneity of circulating GH, the specificity and sensitivity of the primary anti-GH serum (and whether it is monoclonal or polyclonal), the form of the immunoassay (RIA, IRMA), the diluent employed, and the standard used. It is essential that each laboratory measuring GH knows the characteristics of its (immuno)assay and the range of values from "normal" to "abnormal."

The sensitivity of radioreceptor assays (RRAs) for GH is often less than that of the conventional RIA.[7] GH measured by RRA has been considered biologically active, but there are no data to support this conclusion.[8] Since there are 12 or more antigenic sites on the GH molecule that are related to the site of interactions with its receptor, correlation between RRA and immunologic assays may be marginal.[9] Nevertheless, most investigators report reasonable correlations between RRAs and RIAs.[7,10] GH concentrations determined by RRA are somewhat less than those measured by RIA in the same specimen, resulting in an RRA:RIA ratio of 0.75:0.90. The ratio in an individual child is usually stable at rest but may vary slightly during episodes of stimulated GH secretion.[10] Rarely, short children may secrete an immunologically intact but biologically inactive GH molecule, as reflected by a very low RRA:RIA ratio.[11]

Assessment of Growth Hormone Secretion

GH secretion is most often assessed by its secretory response to standard provocative stimuli. Many factors modify the GH secretory response to stimulation. (1) Endogenous GH secretion is inversely related to body mass and provoked GH secretion is depressed in obese subjects, primarily due to an increase in somatostatinergic tone.[12-14] (2) Feeding or administration of glucose blunts the effect of a GH-releasing stimulus; fasting has the opposite effect. (3) A spontaneous surge in GH secretion prior to administration of a provocative stimulus inhibits the challenge response. (4) Drugs may impair (β-adrenergic agonists or β-adrenergic antagonists) or enhance (β-adrenergic antagonists, sex hormones) the effects of a GH-releasing stimulus. The requirement for 2 or more abnormal responses to GH provocative agents in defining the child with classic GHD recognizes the individual variability of response to any single GH stimulus.

A "normal" response to a GH provocative stimulus has been arbitrarily defined at a level that ranges from 5 to 10 ng/mL (RIA). The number selected will depend on the assay employed for measurement of GH and on the assessment of GH secretory responses in *normal* children. Most investigators have selected "normal" values employing data from short children in whom no endocrinologic or systemic disease could be identified. Marin et al[15,16] reported that 20% of a normal population (n=70) had peak GH responses <7 ng/mL (RIA) in response to all stimulatory tests (see Table 1). Indeed, the lower 95% confidence limit of GH response to exercise, arginine, or insulin was 1.5 ng/mL in prepubertal children and 2.9 ng/mL for children in Tanner stage II (breast or male genital) development. Zadik et al[17] reported that 5% of normal prepubertal and adolescent boys and girls studied had peak GH concentrations less than 3.6, 4.0, and 4.5 ng/mL for the 3 provocative stimuli, respectively. Thus, in children of normal stature provoked GH secretion may be relatively low, and the use of any single uniform cutoff value will yield many false-positive results. Estrogen priming of prepubertal subjects increases the GH secretory response to values greater than 7 ng/mL in prepubertal children, comparable to the 95% confidence limit in normal mid- and late-pubertal subjects.[16]

Endogenous GH secretion also can be assessed by determining spontaneous fluctuations in GH concentrations over 6 to 24 hours. Both repeated withdrawal of discrete blood samples and

Table 1: **Mean Peak Concentrations of Growth Hormone in Normal Children and Adolescents After Provocative Stimulation[14,15]**

Tanner Stage	I	II	III	IV	V
Exercise	5.6	8.5	18.2	11.3	17.2
AITT	4.4	7.9	10.0	19.7	26.2
Clonidine	3.0	— 7.0—		— 5.0—	
GHRH	40.0	—53.0—		—65.0—	

AITT, arginine-insulin tolerance test; GHRH, growth hormone-releasing hormone.

the constant exfusion of blood yield levels of mean GH secretion, but frequent,[18] repetitive sampling provides more information about the pattern of GH secretion.[19] Samples collected at 20- to 30-minute intervals have been analyzed for (1) maximal, minimal, basal, and mean GH concentrations; (2) the amplitude, increment, and frequency of GH secretory pulses; (3) the pulse area under the curve of GH release; (4) the GH pulse width, or the interpulse interval; and (5) the production rate of GH. Elaborate mathematical analyses have been developed to examine the secretory patterns of GH (and other hormones).[20] On a daily basis, serum concentrations of GH increase during fasting; during exercise; in response to a psychologic stress; spontaneously without any provocative event; and reproducibly during sleep stages 3 and 4,[18] when there is enhancement of cholinergic tone and repression of somatostatin release.[21,22] Women have higher mean GH concentrations, greater peak GH secretory bursts, and higher basal GH levels than do men.[23]

In the prepubertal child, the production rate of GH increases slightly after 9 years of age, but is relatively similar to that of the adult.[19,24] There is a marked but transient increase in the integrated concentration of GH, the mean GH concentration and the GH production rate in late prepubertal boys and mid-pubertal girls that coincide with the peak height velocity.[13,14,17,19,24-27] Different investigators have reported correlations between the standard deviation score (SDS) for height and the area under the curve (AUC) of GH secretion or the GH secretory rate for prepubertal children,[19,28] the sum of GH pulse amplitude and growth velocity SDS,[29] height SDS and the sum of GH peak areas, and the growth velocity SDS and the logarithm of the sum of GH pulse amplitudes.[30] The pubertal rise in GH secretion has been attributed to the enhancing effects of sex hormones on GH release, and the physiologic consequence is the contribution of GH to the adolescent growth spurt.

How reproducible is the assessment of the 24-hour (or 12-hour overnight) GH secretory pattern in the identification of the GHD subject? Although Zadik et al[27] suggest that the 24-hour integrated measurement of GH is reasonably reproducible, Donaldson et al[31] report that 12-hour overnight mean GH levels fluctuate by as much as –60% to +160% in individual subjects. Is there any diagnostic utility to spontaneous GH measurements? Rose et al[32] reported that only 57% of classic GHD children were identified by spontaneous GH sampling. Similar observations have been recorded by other investigators.[33,34] Donaldson et al[35] reported that the *maximum overnight GH concentrations* were reliable indicators of GH secretion. Pharmacologic stimulation with L-dopa or clonidine led to underestimations of spontaneous GH secretion in 20% of the short children they studied, and measurement of endogenous GH secretion identified the GH-sufficient child more reliably than did standard GH provocative tests. Thus, measurement of spontaneous GH secretion may be helpful in identifying *GH-sufficient* subjects, but in most instances it adds little to provocative tests in the identification of the GHD child.

An exception to the foregoing statement is slowly growing children who received cranial irradiation for neoplasms of the central nervous system; they may demonstrate normal provoked secretion of GH but subnormal spontaneous GH release. These subjects probably have abnormal neurotransmitter regulation of GH secretion, or "growth hormone neurosecretory dysfunction,"[36] and either deficient release of GHRH or excessive secretion of somatostatin, or both. In other patients a similar pattern of GH secretion may reflect decreased mass of somatotropes.

Ancillary Methods for the Assessment of Growth Hormone Secretion

Urinary Growth Hormone

Immunoreactive GH may be measured in urine after dialysis and concentration. Urinary GH excretion is highest in infancy; growing children excrete more GH than do adults when expressed per unit of body weight.[37] In normal prepubertal children, timed overnight urinary GH concentrations range between 1.1 ng/mL and 5.3 ng/night (IRMA)[38] and correlate with peak GH secretory responses to provocative stimuli and with the mean overnight serum GH concentration.[39] Values are low in hyposomatotropic subjects. The absolute mean daily urinary GH excretion shows modest day-to-day variability,[40] but appears to separate normal children and normal short children from subjects with partial or complete GHD (identified by peak serum GH responses to provocative stimuli). On the other hand, overnight (12-hour) urinary GH excretion when expressed per unit of creatinine, does not separate GHD children from normal or idiopathic short-statured children.[39] Thus, the appropriate method for expression of urinary GH values remains undefined. Currently, urinary GH measurements may be useful as screening tests of GH sufficiency/insufficiency but cannot be considered diagnostic studies.

Insulin-Like Growth Factors

Insulin-like growth factor 1 (IGF-1) is GH-dependent; concentrations are low in GHD subjects and high in hypersomatotropic patients. Serum IGF-1 levels are low *in utero* and in infancy, increase with age in both boys and girls, reach maximum values during puberty (earlier and higher in girls than in boys), and decline to adult values as adolescence is completed.[41] Concentrations of IGF-1 correlate more closely with bone age than with chronologic age.[42] However, IGF-1 values are significantly affected by the nutritional status of the individual; they are quite low in malnourished subjects.[43] Furthermore, particularly in very young patients with GHD, IGF-1 values do not reflect the growth-promoting effects of GH; in part, this is likely due to the local secretion and paracrine effects of IGF-1 on cartilage growth.[44] Low values of IGF-1 do not identify the GHD subject with certainty, nor do values within the age- and sex-related normal range exclude the presence of hyposomatotropism. In children with hypopituitarism due to craniopharyngioma, IGF-1 values may often

be normal.[45] Measurement of both IGF-1 and IGF-2 is reported to be more accurate than is the measurement of either alone in the identification of the GHD child.[46]

The urinary excretion of IGF-1 is low in GHD children but values overlap with normal and normal short children.[39] The usefulness of urinary IGF-1 measurements in the identification of GHD children has yet to be determined.

Insulin-Like Growth Factor-Binding Protein 3

The IGFs circulate bound to high molecular weight carrier proteins.[47] The major IGF-binding protein (IGFBP-3) is a 150-kd protein complex of an acid-stable binding subunit, an acid-labile subunit, and IGF. It is inducible by GH and perhaps by IGF-1 itself. Measured by RIA, IGFBP-3 concentrations are low at birth, rise over the first few weeks of life, and then increase slowly with age.[48] There is a significant increase in IGFBP-3 concentrations during adolescence, when levels rise to adult values.[48,49] Maximal IGFBP-3 concentrations are noted approximately 2 years after the peak height velocity of puberty. Serum IGFBP-3 concentrations are below the normal 5th percentile in 97% of hyposomatotropic children and above the 5th percentile in 95% of short children with normal stimulated secretion of GH. Measurement of IGFBP-3 may prove a useful adjunct to the evaluation of the short child, if its generation is consistently independent of IGF-1. If the synthesis of IGFBP-3 is dependent on IGF-1, its utility may be no better than that of the IGF-1 measurement itself.

Growth Response to Growth Hormone

Nearly 40% to 60% of healthy short children with normal GH secretory responses to provocative stimuli will respond to the administration of human GH with an increase in growth rate more than 2 cm/year above basal values during the first year of therapy.[50] In the author's experience, the best predictive measurement of subsequent response in such non-GHD children is the pretreatment growth rate — the more slowly a child is growing, the more likely it is that the child will experience a substantial, short-term (1-year) acceleration of growth rate when treated with GH.[51] Thus, the short-term linear growth response to GH cannot be used to identify the GHD subject.

Conclusion

Classic GHD is a discrete entity, and is characterized by defined clinical, radiographic, and endocrinologic criteria. Children with partial or subtle defects in the secretion of GH are difficult to identify, and no individual assessment of GH secretion or GH-associated biochemical finding unerringly detects such subjects.

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IS GROWTH HORMONE DEFICIENCY A DISCRETE ENTITY? AGAINST THE NOTION

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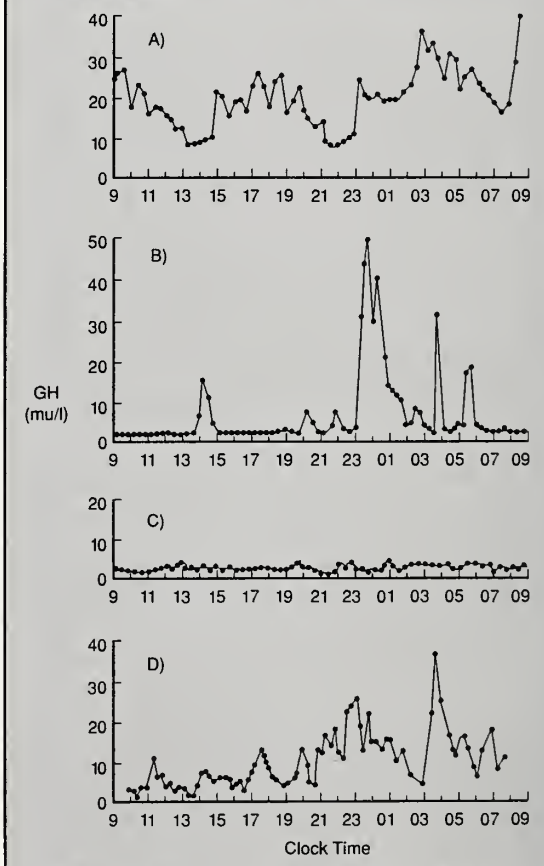
Introduction

Historically it had been believed that there was a single cutoff level of peak stimulated growth hormone (GH) secretion that could distinguish children with GH deficiency (GHD) from normal children. At a later time it was appreciated that the problem was not as simple as that, and 3 categories of patients could be described by peak GH response to a pharmacologic stimulus: GHD children, children with partial GHD, and normal children. Surprisingly, it was believed that such cutoff levels of GH secretion were independent of age, sex, and puberty. It has become apparent that GHD does exist, but it is a state of absent GH secretion in association with GH gene deletion or abnormalities of gene expression. The more common situation is GH insufficiency, in which there are varying degrees of abnormal GH secretion. It is now appreciated that there is a wide spectrum of abnormalities among children with classic GHD, and that the majority of such children satisfy the criteria for GH insufficiency. Such is this spectrum, and the enormous difficulty of interpreting individual peak GH concentrations, that in countries such as Australia the selection of patients for GH administration is based purely on anthropometric grounds and is totally independent of either pharmacologic or physiologic tests of GH secretion.[1] In other words, the truth be known, I don't know what biochemical GHD is.

Growth of Normal Children

The centile lines for normal children on a "distance" growth chart are not parallel, but diverge with time. Thus, tall children grow at a higher centile velocity than short children. Interestingly, tall children produce more GH than short children (See Figure 1),[1] and this may explain why the former grow at a faster rate than the latter.[2,3] Does a child growing abnormally and demonstrating abnormal GH pulsatility (with normal peak GH values) have GH insufficiency? I propose that he/she does. The infancy-childhood-puberty model of growth[2] provides a useful mechanistic concept for the control of growth. During the middle childhood years, growth progressively decelerates and is dependent predominantly on GH secretion. It would be surprising if normal children produced the same amount of GH at the age of 3 and 4 years as between 8 and 9 years. Growth during the pubertal growth spurt depends on both GH and sex steroids; one without the other produces inadequate growth acceleration.[3]

Figure 1: **Variability in the Pattern of Physiological GH Secretion**



Four serum profiles of 24-hour endogenous GH secretion from four 6-year-old boys. Top (A), child with pituitary gigantism growing at 7 cm/year. (B), normal tall boy growing at 7 cm/year. (C), boy with GH deficiency growing at 3 cm/year. (D), boy with dysfunctional GH secretion growing at 4 cm/year (note lack of return to baseline values between pulses).

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Patterns of Endogenous Growth Hormone Pulsatility

GH responses to a battery of pharmacologic tests probably represent short-term metabolic changes, rather than demonstrating any relevance about the relationship between growth and GH secretion. In recent years, great interest has been expressed in the interpretation of physiologic GH secretion and growth. There has been considerable controversy about the relative importance of pharmacologic and physiologic tests of GH secretion,[4] especially in relation to the selection of patients who may respond to GH treatment. However, 24-hour patterns of endogenous GH secretion have enabled us to study GH pulsatility, and we have come to realize that there is even greater variation of GH secretion than could be appreciated by the results of pharmacologic tests.

Numerous patterns of endogenous GH secretion have been described, such as the predominantly single pulses seen in children with Turner syndrome and Russell-Silver syndrome.[5] Many children have GH pulses that do not return to immeasurable concentrations between pulses. Persistently high levels of GH secretion and the absence of a characteristic pulsatile pattern have been described in adults with acromegaly and children with pituitary gigantism. (See Figure 1.) Although children with tall stature may have higher peak levels of GH, mean concentrations will be considerably lower than those seen in patients with pituitary gigantism or acromegaly. It has been appreciated for many years that some children with abnormal growth had normal GH concentrations in response to pharmacologic tests. However, physiologic studies have revealed that such children have a dysfunctional pattern, that is, an absence of discrete GH pulses. Such patterns have been described as neurosecretory dysfunction by Spiliotis and colleagues,[6] although this latter term has come to have different meanings.

By the use of such physiologic tests, we have come to realize that the spectrum of GH secretion is far greater than can be appreciated by peak GH concentrations achieved in response to pharmacologic tests. There is a whole range of different patterns of GH pulsatility, although many of these are poorly understood in relation to the pattern of growth observed.

Growth in Growth Hormone Deficient Children and Response to the Growth Hormone Treatment

The greater the degree of GH insufficiency, the slower the rate of growth and the greater the initial response to GH treatment.[7] There appears to be no distinct cutoff level that can be determined by peak GH levels found in either physiologic or pharmacologic tests.[4] There is very little evidence that GH responses to provocative stimuli of 7, 10, or 15 ng/mL represent distinct clinical conditions. Children with minor degrees of GH insufficiency and short normal children do have increased growth rates in response to GH treatment, but the response is much less dramatic than in children with classic GHD.

Growth Hormone Secretion During Puberty

During late prepuberty in both sexes and in early puberty in boys, there is a gradual growth deceleration. This is associated with physiologic GH insufficiency. At the onset of the spontaneous growth spurt, or if exogenous sex steroids are administered, normal GH secretion results.[8] Studies using pulsatile gonadotropin-releasing hormone (GnRH) to treat children with hypogonadotropic hypogonadism have revealed that it is the change in GH secretion, not sex steroid secretion, that correlates with changes in growth rate during puberty in both sexes.[9] In girls, there is a dramatic increase in GH pulse amplitude with the onset of breast development; in boys, the increased pulse amplitude does not occur until a 10-mL testicular volume (genitalia stage 3 to 4) has been attained. Certainly there is no single peak GH level that can be considered normal during the pubertal growth spurt, as the confounding factors of sex and stage of pubertal development need to be defined as well.

Psychosocial Dwarfism

The characteristic biochemical feature of children with psychosocial dwarfism is hypopituitarism (most commonly GH insufficiency) that reverses with a change of environment.[10] If a child with psychosocial dwarfism is admitted to hospital without parental access, serial physiologic tests of GH secretion will reveal a gradual (but transient) change from organic GHD or GH insufficiency to normal GH secretion during a period of 2 to 3 weeks.[11] Although the patterns of GH secretion are similar between different profiles, there is no sudden change between insufficient and normal GH secretion; there is, however, a gradual increase of pulse amplitude from insufficient to normal GH secretion.

Low-Dose Cranial Irradiation

The treatment of children with low-dose cranial irradiation—for example, 1,800 or 2,400 cGy administered for prophylaxis of meningeal involvement in acute lymphoblastic leukemia—may induce a dual endocrinopathy in girls.[12] Such girls may have both precocious puberty or early pubertal maturation and GH insufficiency. During the onset of pubertal development, sufficient GH secretion may be present to allow a normal rate of growth for chronologic age, although not allowing for the stage of pubertal development. Such a biochemical lesion of GH secretion has been demonstrated.[13] Thus, a normal growth rate during late prepuberty may be attained, although there is insufficient GH secretion to permit an adequate growth spurt during puberty.

Neuroradiologic Assessment in Children With Growth Hormone Deficiency

Just as there is a continuous spectrum in biochemical assessment of GH secretion, there is a spectrum of pituitary morphologic lesions in children with GHD. This may range from pituitary aplasia to hypoplasia,[14] although there appears to be no definite relationship between morphologic appearance and endocrine secretion. However, children with pituitary hypoplasia are more likely to have "isolated" GH insufficiency, while those with pituitary aplasia may have evolving multiple pituitary hormone insufficiency.

Summary

I do not believe GHD to be a distinct entity, but rather a spectrum of disorders of GH pulsatility. The notion of a discrete cutoff level of GH secretion (either pharmacologic or physiologic) to distinguish the GHD from the normal, is purely historical and has no relevance to modern pediatric endocrinology. GH secretion is a continuum.

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DISCUSSION I: A & B

A. Methods of Assessing Growth Hormone Secretion and Determining Growth Hormone Deficiency - Allen Root, MD

B. Is Growth Hormone Deficiency a Discrete Entity? Against the Notion - Richard Stanhope, MD

Moderated by Jo Anne Brasel, MD

FRASIER: We incorrectly use the words "identify," "distinguish," and "define" in describing tests for growth hormone deficiency. The purpose of a laboratory study is to confirm or disprove a clinical perception. When we try to extend the use of a laboratory test beyond confirming the clinical diagnosis, it does not work and then we are disappointed.

LIPPE: I would like to offer an important point: If we do not perform any of these diagnostic studies, we will miss patients with organic diseases that have other consequences. Just because a child is short and slow growing and appears to match the clinical criteria of growth hormone deficiency, it does not mean that you do not want to know that the child has a brain tumor or inflammatory bowel disease, Turner syndrome, or some other disorder which needs to be addressed. If we are not going to evaluate *why* a child is growing slowly and our main goal is only try to treat the "symptom" with growth hormone, we will miss the other pathology. We could do a serious disservice if we choose to ignore the diagnostic relevance of testing procedures and miss other illnesses.

STANHOPE: I totally agree, but I do not do an insulin tolerance test to look at growth hormone secretion. I do it to look at cortisol levels. It is the growth *rate* that tells you about the need for GH, not the GH *level*.

CHARO: Please clarify what a "normal growth hormone" level means. Is it supposed to reflect a global mean and standard deviations from that mean? Or is "normal growth hormone" supposed to be reflective of specific racial groups, nutritional status, sex, age, etc? I am not sure I understand what you are communicating.

ROOT: This has been a major problem. Many studies in the literature have not identified their control group children as normal by various (defined) growth parameters. These data are now appearing in the literature, as we pointed out, and they show extreme variability of growth hormone secretion in normal children.

LANTOS: Dr. Stanhope, if I understand you correctly, your advice to practicing endocrinologists today would be that there is no point in ever measuring growth hormone level. Is that a misunderstanding?

STANHOPE: I do not think that this is far from the truth. That is my personal opinion, but you will hear very different answers from around the table. Measuring the child and tracking their growth rate and velocity is the best thing we can do for them. With many of these children, you will find that you really do not have to do much because they are growing better than you had been informed.

FRASIER: One issue is the practice of good clinical medicine and the making of an appropriate diagnosis. Another issue is deciding what to do about someone who is short. We cannot mix up these 2 issues.

GERTNER: I think it is also rather dangerous to be too much of a "lumper" and merge all cases together. In my view, there certainly is such a thing as growth hormone deficiency, and I found it quite amusing that Dr. Stanhope was showing a slide during his presentation and saying, "This patient clearly has organic growth hormone deficiency." If a person, for example, has a genetic inability to make growth hormone because of a mutation of the growth hormone gene, or if the person's pituitary gland is destroyed, then clearly they are growth hormone deficient. There is no argument about that. The problem that we are facing is that growth hormone deficiency, like hypertension or obesity is a disease of gradation (unlike pregnancy which you either have or you do not), and we need to know where to draw the line.

ALLEN: Dr. Stanhope, you did not show the data describing the relationship between the sum of growth hormone pulse amplitudes and growth velocity in short children. Nor did you say that you believe in the continuum of growth hormone. But I wonder, do you?

STANHOPE: I do believe in the entity, but, of course, we do not have the data to prove it.

BRASEL: I agree with both Drs. Root and Stanhope that there really is an entity of growth hormone deficiency. Cranial radiation studies show us that there is a gradation of growth hormone deficiency with a stage of very low spontaneous GH secretion but normal responses to stimulation tests. When those children are followed further, their provocative tests fail and they have very low secretion of growth hormone. These children are truly growth hormone deficient. The difficulty of using spontaneous secretion studies and urinary growth hormone, or any of several other approaches, is due to the fact that normal children have such low levels from time to time, it is very difficult to distinguish normal from below normal. I could show Dr. Stanhope the growth hormone profiles of perfectly healthy, normally growing children and they would match the profiles that he is interpreting as insufficient growth hormone. Consequently, it is this variability that makes the overnight spontaneous studies less diagnostic than we would like them to be. We wanted them to be definitive, but they have not proven to be so because normal children have similar patterns.

WEISBARD: I find myself continuing to be confused by the notion of growth hormone deficiency as a single discrete entity. Let me ask the question in a slightly different way: Is there a recognized diagnostic status that correlates well with responsiveness to growth hormone therapy—that is, defining the status by responsiveness to the potential intervention? And precisely what relationship does that diagnostic status bear to the discrete entity of growth hormone deficiency?

BRASEL: That just happens to be the next question.

EFFICACY OF GROWTH HORMONE THERAPY IN PATIENTS WITHOUT CLASSICALLY DEFINED GROWTH HORMONE DEFICIENCY

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Introduction

The ethical dilemma we are discussing exists because growth hormone (GH) therapy is indeed effective in short children without classically defined GH deficiency (GHD). We think it is reasonable to conclude that endocrinologists would not use an extremely expensive and potentially dangerous treatment in generally healthy children unless it were effective. In this paper, we present data supporting the notion that alternative conclusions are not likely, namely that pediatric endocrinologists are deluded, or simply too hopeful, about GH therapy in non-GHD children.

In our clinic, we often entertain the idea of instituting specific auxologic criteria to treat any prepubertal patient, regardless of stimulated GH levels, by utilizing some combination of low height standard deviation score (SDS), subnormal growth velocity, and predicted adult height (PAH) below a certain level. The last 2 criteria are helpful in distinguishing patients with constitutional delay, who then might receive alternative therapy. Several assumptions are inherent in the suggestion that we initiate therapy in any patient meeting certain criteria. (1) Our decision to institute GH therapy generally rests upon auxologic criteria alone and ignores the results of GH testing, except when the clinical criteria are only marginally met. (2) Neither clinical criteria nor laboratory measures, including GH levels, are particularly helpful in predicting individual response to GH. (3) Sufficient evidence exists that GH therapy of non-GHD patients is effective enough to warrant its use. The role of GH testing in defining GHD is presented in another paper. The third statement is the topic of this paper, with some pertinent data concerning the second statement. We will concentrate on the data from children with idiopathic short stature (ISS, also referred to as normal variant short stature, or NVSS) and with Turner syndrome (TS). These are the 2 populations that we and other investigators have most extensively studied.

Raben[1] was the first to report a short-term trial of pituitary-derived human GH in short children without GHD, demonstrating an increase in growth rate from 3.5 to 8.0 cm/yr. Tanner et al's report of long-term GH treatment in 55 children included patients with GHD, intrauterine growth retardation, TS, and ISS, among others.[2] The limited success in treatment of non-GHD patients in the Tanner et al study and some of the other early trials has been retrospectively attributed to relatively infrequent GH administration or low doses. By the mid-1980s, however, many studies utilizing pituitary-derived GH in children with normal provocative test results had established a short-term response to GH. For instance, in one 6 month trial, 10 short children unselected for pretreatment growth rate all increased their growth rate in response to GH administered 3 times a week (TIW), with a mean increase from 4.3 ± 0.3 to 7.4 ± 0.5 cm/yr.[3] In a final report from the National Hormone and Pituitary Program Growth Hormone Committee prior to discontinuation of pituitary derived GH, 45 of 48 children with growth rates <4 cm/yr and normal provocative test results had an increase in growth rate during a 6-month trial (mean change, 3.4 to 6.9 cm/yr).[4] Therefore, even before the introduction of recombinant GH, a significant short-term response to GH had been demonstrated in individuals with ISS.

Investigations utilizing recombinant GH have uniformly confirmed the short-term response. The advent of recombinant GH has changed the limiting factor in GH treatment from the GH supply to financial cost, or, rather, to the cost-benefit ratio as defined by the patient's family and physician, and by society in general. It has also allowed for studies of larger, more homogeneous numbers of each class of potential GH candidates and raised the hope that subsets of responders could be delineated, preferably prospectively. Attention in these studies now focuses on the questions of final height, the timing and efficacy of GH therapy in relation to puberty, possible complications, potential predictors of response, and criteria for treatment.

Growth Hormone Treatment in Children With Idiopathic Short Stature

The US Genentech Collaborative Study Group has enrolled 121 children with ISS and is now in its fifth year.[5] Inclusion criteria

included age >5 yr, height < –2.5 SDS, serum GH >10 ng/mL, and bone age <10 yr for boys and <9 yr for girls. Notably, pretreatment growth rates were not the basis of selection, although most were below the 50th percentile. Patients receiving GH 0.1 mg/kg TIW demonstrated an increase in mean growth velocity in the first year from 4.6 ± 1.1 to 7.5 ± 1.2 cm/yr.[8] There was no detectable difference in growth rate increment between those classified as having familial short stature and those with constitutional delay. A first-year randomized control group exhibited no significant change from the pretreatment growth rate and no change in PAH.

In the second year, both the control and treatment groups were randomized to either TIW or daily treatment groups (both received GH 0.3 mg/kg/wk, with adjustment for weight change). Seventy-five children have now completed 3 years of treatment, and the majority have entered puberty. These results are shown in Table 1, and daily and TIW treatment groups are considered together. However, 3-year cumulative growth response did correlate with dosing frequency, with a higher increment in mean growth velocity SDS and PAH in the daily administration group, consistent with the consensus from other GH studies. Analyzing growth rate for bone age, only 8% of subjects were above the 50th percentile during the pretreatment period. In successive years of treatment, 94%, 70%, and 63% of children were above the 50th percentile for growth rate.

Table 1: **Growth Velocity, Height SDS, and PAH SDS During 3 Years of TIW or Daily GH Therapy (US Genentech Collaborative Study Group)**

	Pretreatment	Year 1	Year 2	Year 3
n	103	103	103	75
Growth velocity (cm/yr)	4.6 ± 1.3	8.0 ± 1.4	7.5 ± 1.8	7.0 ± 1.8
Height SDS	–2.7 ± 0.5	–2.2 ± 0.6	–1.9 ± 0.7	–1.7 ± 0.7
PAH SDS	–2.7 ± 0.9	–2.0 ± 1.1	–1.8 ± 1.0	–1.6 ± 1.2

There was no relationship between response to GH and either baseline 12-hour GH secretion or provocative GH levels, nor did growth response correlate with baseline height, bone age, growth rate, or parental heights. While first-year growth rate SDS was predictive of second-year response, correlation with third-year response was weak. There was no correlation of duration of GH therapy with either the age of onset of puberty or the rate of pubertal advance. Thus, we have concluded from the 3-year data that GH therapy in ISS significantly improves mean SDS for growth rate, height, and predicted height without altering pubertal progression. Unfortunately, we have found no clear predictor of response.

Ongoing European studies of GH treatment of ISS have confirmed many of the US results. Albertsson-Wikland in Sweden has treated 40 prepubertal children for 1 year and 24 children out to 4 years with daily GH.[6] In the 1-year data, mean height velocity increased from 4.6 to 7.5 cm/yr, and 80% exceeded a 2-cm increment. In contrast with the US data, there was an inverse relationship between either pretreatment growth rate or GH secretion and the growth rate during treatment, suggesting that these baseline factors might determine the likelihood of response. In the multi-year treatment, growth rate improved from a pretreatment 4.2 cm/yr, to 8.1, 6.7, 6.0, and 4.9 cm/yr over successive treatment years. Furthermore, in the period following discontinuation of treatment, mean growth rate was 5.1 cm/yr, contradicting the concern that growth rate off treatment might fall below the pretreatment rate ("catchdown" growth). At a recent meeting, Albertsson-Wikland reported 2-year treatment results in 52 prepubertal children whose mean height SDS increased from –2.9 to –2.0. Her analysis suggested that the final height of 33 children depended upon the timing of treatment prior to puberty, with less improvement (+0.3 height SDS) when therapy was initiated just prior to peak height velocity than with initiation 4 years prior to the peak of puberty (+0.7 height SDS). This stratification in response has not been confirmed in other studies.

The Dutch Growth Hormone Working Group has treated prepubertal children with ISS using criteria of height SDS < –2.5 and height velocity <25th percentile for bone age, ie, slowly growing short children, in a randomized study with controls in the first year and allowing for an increased daily dose in poor responders (<2 cm/yr in the first year or <50th percentile in subsequent years).[7] Mean velocity decreased from 7.6 cm/yr in the first treatment year to 5.1 cm/yr in the second year when the dose remained unchanged (n=11). The majority of 21 children who have completed 4 years of therapy required a doubling in dosage to maintain a growth rate >50th percentile. There were no differences in growth response between prepubertal subjects and those who had entered puberty. After 4 years, mean height SDS was significantly increased, but mean bone age advancement was approximately 1.2 years per treatment year. Mean increase in PAH was thus +0.5 SDS. In another study, Hindmarsh et al[8] in London have treated 16 children, including those with normal pretreatment growth velocities, for 3 years. Height velocity SDS increased from –0.44 to +2.20 (5.3 to 7.4 cm/yr) in the first year, then dropped to +0.74 in year 2, before rising again to +1.96 with an increase in dose during year 3. PAH significantly increased in boys (+6.8 cm) and girls (+4.2 cm).

Growth Hormone Treatment in Children With Turner Syndrome

Although promising studies of GH treatment of chronic renal failure and intrauterine growth retardation (IUGR) are in progress (reviewed in reference 9), the other group of subjects with short stature in which large and convincing studies have been published is TS. Girls with TS appear to have a skeletal dysplasia rather than GHD or GH secretory dysfunction, although the latter has been reported. Turner girls have a slow growth rate throughout childhood, a continued decline through adolescence, and significantly delayed epiphyseal fusion, presumably attributable to ovarian failure.[10] They are an ideal population for GH trials in that the syndrome is easily verifiable

and that spontaneous puberty does not abbreviate treatment or complicate interpretation of therapeutic success as it does in ISS. The first large prospective clinical trial of GH in TS began in 1983 and is currently in its eighth year.[11,12] In this study, 70 girls ranging in age from 4.7 to 12.4 years, with TS and normal provocative GH testing, were randomly assigned after a pretreatment period to 1 of 4 groups for the first 12 to 20 months: (1) control (no treatment), (2) oxandrolone (0.125 mg/kg/d), (3) methionyl-GH (0.125 mg/kg TIW), and (4) combination of oxandrolone plus methionyl-GH. Subsequently, all groups except group 3 received therapy with combination oxandrolone (0.0625 mg/kg/d) and methionyl-GH; group 3 continued to receive methionyl-GH alone.

Growth data for the first 4 years of treatment are expressed as growth velocity SDS for untreated TS patients (derived from the Lyon European standard curve[13]) in Table 2. The response in height velocity to GH or combination therapy declined over successive years, but in all years was still greater than the pretreatment velocity, as has been the experience with GH use in subjects with GHD or NVSS. Because this decline in growth velocity is partially attributable to the natural age-associated decline characteristic of Turner syndrome, the most telling way of expressing the data is by height velocity SDS relative to an untreated TS population. (See Table 3.) Combination GH and oxandrolone therapy was even more effective than GH alone. However, approximately 30% of subjects on the higher dose of oxandrolone exhibited virilization, and many

Table 2: **Annual Growth Rate of Turner Patients (cm/year)**

Group	Prestudy	Year 1	Year 2	Year 3	Year 4
1. **Control → Combination**	4.2 ± 1.1	3.8 ± 1.1	8.3 ± 1.2*	6.7 ± 1.4*	
2. **Oxandrolone → Combination**	4.1 ± 1.9	7.6 ± 1.5*	7.1 ± 1.6*	5.3 ± 2.4*	
3. **Methionyl-hGH**	4.5 ± 0.8	6.6 ± 1.2*	5.4 ± 1.1*	4.6 ± 1.4	5.5 ± 1.5*
4. **Combination**	4.3 ± 0.9	9.8 ± 1.4*	7.4 ± 1.4*	6.1 ± 1.5*	4.9 ± 1.5

Data are expressed as mean ± SD. Year 2 represents the first year of phase 2 for groups 1 and 2; this phase began 12-20 months after the beginning of year 1. After year 1, oxandrolone was lowered from 0.125 to 0.0625 mg/kg/day. At year 4, data for all combination therapy groups are grouped together.

* Significantly greater than the annual growth rate for the control group in year 1 ($P<0.05$). The annual growth rate for group 4 (combination) is significantly greater than for group 3 (methionyl-hGH) for each of the 3 years ($P<0.05$). Adapted from Rosenfeld et al.[11,12]

Table 3: **Height Velocity Standard Deviation Scores Of Turner Patients**

Group	Pretreatment	Year 1	Year 2	Year 3	Year 4
1. **Control → Combination**	0.2 ± 1.2	- 0.1 ± 1.0	5.5 ± 1.4	4.0 ± 1.7	
2. **Oxandrolone → Combination**	0.2 ± 1.0	4.4 ± 1.8	4.2 ± 1.5	2.4 ± 2.3	
3. **Methionyl-hGH**	0.5 ± 0.8	3.1 ± 1.2	2.0 ± 1.1	1.4 ± 1.5	2.9 ± 1.4
4. **Combination**	0.2 ± 0.9	6.6 ± 1.2	4.3 ± 1.4	3.0 ± 1.4	2.7 ± 1.3

Growth velocity SD scores are presented as mean ± SD in comparison with untreated Turner patients derived from Ranke.[19]

investigators are wary of the effect of long-term oxandrolone therapy on final height. After 3 years of treatment with GH alone, the increment in bone age was 2.73 ± 0.72 years; 3 years of combination treatment resulted in an increase of 4.05 ± 1.23 years. Nevertheless, the mean PAH of the combination group is greater than that of the GH group, leaving open the question of the usefulness of oxandrolone in the treatment of short stature associated with TS.

The results of this study clearly demonstrate that GH, either alone or in combination with oxandrolone, significantly accelerates growth for a period of at least 4 years. Thirty subjects who have completed therapy (from all groups) have a mean final height of 151.9 cm, compared with initial PAHs (Bayley-Pinneau) or projected adult heights (Lyon growth curves) in the range of 143 cm to 144 cm. In spite of this apparent improvement in final height, we feel the study may actually underestimate potential benefit from GH therapy, since the relatively advanced degrees of skeletal maturation at initiation of therapy probably limited the length of potential treatment. Our current policy is to discuss GH therapy with all TS families and to offer treatment when the patient falls below the 5th percentile for normal girls, which usually has occurred by the time a patient is referred to our clinic. Initial treatment is with GH alone, at a dose of 0.05 mg/kg/d. Currently available data are inadequate to assess the most effective dose of GH, although data suggest that a higher growth rate is observed with daily administration, as with therapy of GHD or ISS. These findings from the initial trials of GH in TS have been confirmed in studies from Europe and Japan.[14-18]

Discussion

The North American and European trials of GH in ISS and TS have provided abundant evidence that GH therapy is effective in significantly improving mean growth velocity for 1 or more years. However, the duration of most published studies has been 2 years or less. In 2 of the largest current studies (United States and Sweden) in ISS, after a dramatic increase in mean height velocity in the first year of treatment, there has been a gradual decline in growth velocity in the second and third years. Nonetheless, the mean growth rates even in the third year were 3.4 cm and 2.8 cm/yr greater than the pretreatment rates in these respective studies. In the Dutch and British experience, growth rates in the later years could be maintained by increasing the GH dose. Thus, it would appear that a significant increase in mean growth velocity increment can be maintained for at least 3 years in ISS patients. In fact, the cumulative growth response is comparable to that seen in GH treatment of GHD, giving rise to the argument that GHD and non-GHD subjects cannot be differentiated on the basis of growth response. One inference of such a conclusion is that the treatment decision should not discriminate between GHD and non-GHD patients, since average treatment outcome is similar.

In TS, only the US study has proceeded several years. The difference between pretreatment and first-year growth velocity with GH therapy alone (administered TIW) was smaller than those seen in GHD and ISS trials, although several other Turner studies have documented a greater first-year increment. Nonetheless, in the third and fourth year of the Genentech Turner study (daily GH administration), the growth rates were still +1.4 and +2.9 SDS above the standard Turner curve. Therefore, a sustained increase in growth velocity can be induced by GH therapy in either ISS or TS.

Final height data, however, are preliminary in both ISS and Turner trials, and we still must largely rely upon changes in PAH rather than final heights in most studies. In the US collaborative ISS GH study, for instance, only predicted heights are available; mean PAH SDS has improved from –2.9 to –1.6. The Swedish and Dutch groups have reported preliminary final heights in treated ISS, with an improvement of only about +0.5 height SDS over predicted height. Final height data are more impressive in the American Turner study. In this study, 82% of TS subjects still receiving GH and 91% of subjects receiving GH and oxandrolone have already surpassed their PAHs. Those who have completed therapy have added a mean 8 cm to 9 cm over the mean final height in the Turner standard curve.

Several points need to be elaborated here. First, since none of the major studies has an untreated control group throughout the duration of treatment, interpretation of final heights is dependent upon pretreatment PAHs or, in the Turner study, an untreated control outside of the study. We cannot soon look forward to any study resolving the question of final height in a comparison of randomized treated and untreated subjects. Second, therapy historically has been initiated at a relatively advanced age (as in the studies described), which argues that earlier onset of therapy might lead to a substantially greater benefit in final height than demonstrated in studies, particularly since response may be greater at younger ages. Furthermore, even many ongoing studies are utilizing TIW dosing, which is now recognized as inferior to daily administration. Thus, potential treatment response may be underestimated by most studies. Against this, we should add that short-term studies could be biased to overestimate response, in that slow pretreatment growth rates may demonstrate some regression to the mean. Third, final height is not the only measure of treatment success. Some advocates of GH therapy argue that anabolic effects, prevention of further loss of height potential, and the psychologic benefits of improvement in height SDS or growth velocity SDS are great enough to justify therapy. However, few data exist to support such contentions.

Current data are not sufficient to predict the kinds of GH regimens that might be recommended in the future. We have little information on appropriate dosing. If further studies demonstrate that the decline in growth rate in later years of treatment approaches baseline rates, stepwise dose increases may be needed. It is plausible that therapy could be limited to a few years. Similarly, if it is determined that GH therapy during puberty is ineffective, it might be discontinued earlier than is the current practice; on the other hand, substantially higher doses of GH, mimicking the physiologic surge in GH secretion rates,

might be effective during puberty. Alternatively, luteinizing hormone-releasing factor (LRF) analogues to delay puberty may provide the opportunity to extend GH therapy when short stature is severe. It remains to be determined whether oxandrolone or another androgen, certainly less expensive than GH, will play a role in future therapies.

It is important to remember how much individual variability is implicit in changes seen in mean growth velocity or mean height during GH therapy. Clearly, some subjects demonstrate dramatic responses, while others exhibit little change in growth velocity even in the first year of therapy. Obviously, the number of children entered into therapy could be significantly reduced if accurate predeterminants of response were available. Unfortunately, preliminary results of the Genentech Collaborative Study Group study have not established any useful predictor of response. At the moment, the change in height SDS during a 12-month treatment period is the best predictor of longer term response. Although some investigators have reported that pretreatment growth rate is inversely related to treatment response,[9] other studies, including the Genentech Collaborative Study Group, suggest that pretreatment growth rate and height SDS are not helpful. Correlations of height velocity change during treatment with baseline GH secretion rate, baseline serum insulin-like growth factor I (IGF-I), or short-term IGF-I increase[6] have been contraindicated by several studies. Therefore, a predictor of growth response reliable enough to eliminate some patients from treatment consideration remains to be established.

In summary, studies in both ISS and TS demonstrate that GH significantly improves mean growth velocity over several years. Mean PAH is increased, and preliminary data in both populations suggest that final height will be improved. In TS, where the natural history and height outcome are well-documented, GH therapy seems to us clearly justified by the available data. The natural course of the heterogeneous ISS group is more obscure and leads to more tentative conclusions. Assuming that the preliminary final height data in GH treatment of ISS are confirmed, we can restate one aspect of the ethical dilemma: GH treatment clearly benefits some patients with ISS, but not others. Unfortunately, there are currently no useful criteria other than a treatment trial to predict which patients with normal provocative GH levels will respond to GH.

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GROWTH HORMONE IS NOT EFFECTIVE IN NON-GROWTH HORMONE DEFICIENT PATIENTS

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Introduction

I have been assigned the task of presenting the negative position regarding the effectiveness of growth hormone (GH) therapy in patients who are not GH deficient (GHD). I have eliminated from consideration the treatment of children in whom short stature (SS) is associated with any particular syndrome and have chosen to limit this presentation to the effect of GH in children who are short but otherwise normal. Although such children have been grouped under a number of confusing headings, I will ignore this unsatisfactory terminology and refer to them as having simply non-GHD SS. I have attempted to review the literature pertinent to this group of patients and to draw conclusions supported by this information.

I will not argue that there is no initial acceleration of growth in non-GHD patients receiving therapy. The literature is essentially unanimous in demonstrating positive short-term results. There are now several reports of the effect of GH given for 1 year on the height velocity of short children in whom no significant abnormality of GH secretion can be demonstrated.

Review of Data Regarding Growth Hormone Treatment in Non-Growth Hormone Deficient Children

Hindmarsh and Brook[1] followed 26 short prepubertal children for 2 years; during the second year, 16 were given 2.0 IU GH 6 times each week. When compared with 10 untreated control patients, height standard deviation score (SDS) and growth velocity SDS for both chronologic age (CA) and bone age (BA) were significantly improved. The average growth velocity increased from 5.3 to 7.4 cm/year. Albertsson-Wikland[2] has followed a relatively large number of short children with normal GH function while they received GH 0.1 IU/kg daily. She treated 40 such children for 12 months, during which their height velocity increased from 4.6 ± 1.1 (SD) cm/year to 7.5 ± 1.3 (SD) cm/year. In 80% of those treated, height velocity increased by at least 2.0 cm/year.

Wit and the Dutch Growth Hormone Working Group[3] have reported their first-year experience with GH in short normal children. These investigators administered GH 2 IU/m^2/day to 20 prepubertal children who were at least 2.5 SD below the mean height for CA and were growing below the 25th centile for height velocity for BA. BA was <10 in girls, and <11 in boys. Peak GH responses to standard stimuli exceeded their cutoff point for GHD. They also followed a control group of 10 similar children who were untreated. Height velocity during this year of therapy increased from 4.3 ± 1.4 (SD) cm/year to 7.3 ± 1.1 (SD) cm/year. There was no change in the mean height velocity of the control group. The increase in height velocity exceeded 2 cm/year in 11 treated children (55%).

The Genentech Collaborative Study Group[4] reported an analysis of the first 12 months of a study in which 63 short (height below the 3rd percentile for age) children who showed normal GH concentrations in response to standard provocative tests of GH reserve received GH 0.1 mg (0.26 IU)/kg TIW and 58 similar children served as a control group. Children with dysmorphic features, low birth weight, or an illness that could interfere with growth were excluded. Growth velocity was not used as an inclusion criterion. Assignment to the treatment or control group was random. The growth velocity of 50 treated prepubertal children increased from 4.7 ± 1.2 (SD) cm/year to 7.3 ± 1.2 (SD) cm/year while that of 40 prepubertal control children did not change. In 35 treated patients (70%) growth velocity increased by at least 2.0 cm/year. The height SDS of treated children changed from –2.7 ± 0.5 (SD) to –2.2 ± 0.6 (SD) after 12 months of GH administration. There were no differences in the responses of children classified as having genetic SS and those classified as having constitutional growth delay. Two additional groups of children also have now received GH for 1 year.[5] Twenty-four children who were given GH 0.1 mg/kg TIW increased their growth velocity from 5.1 ± 1.6 (SD) cm/year to 8.2 ± 1.4 (SD) cm/year and 23 children who were given GH 0.04 mg/kg/d increased their growth velocity from 4.7 ± 1.2 (SD) cm/year to 9.0 ± 1.6 (SD) cm/year.

Cowell and the Australasian Paediatric Endocrine Group[6] have presented the Australian experience in which 37 children receiving GH 0.6 IU/kg/week increased their growth velocity to 8.7 ± 1.8 (SD) cm/year and 40 children given GH 1.2 IU/kg/week increased their growth velocity to 10.8 ± 1.8 (SD) cm/year . Twenty-seven placebo-treated children did not have a significant change in growth velocity. Lesage et al[7] recently

reported that high-dose (0.3 IU/kg/d) GH increased growth velocity in 10 French children from 4.0 ± 0.3 (standard error [SE]) cm/year to 10.7 ± 0.6 (SE) cm/year.

Little data are available that allow conclusions regarding the effect of GH therapy in non-GHD children beyond the first year of treatment. Thus far, they do not point the way to firm conclusions regarding long-term effectiveness. The Genentech Collaborative Study Group[5] has presented data accumulated at the end of 2 years of treatment in their original study patients. During the second year of therapy, half received the same dose of GH (0.1 mg/kg TIW) and half received a weekly dose equivalent to 0.04 mg/kg/d. The growth velocity of patients receiving GH TIW fell from 7.5 ± 1.1 (SD) cm/year to 6.8 ± 1.8 (SD) cm/year. The growth velocity of the patients who were changed to daily treatment was maintained essentially unchanged at 7.8 ± 1.4 (SD) cm/year.

Hindmarsh et al[8] have analyzed the response of their 16 patients after 3 years of therapy. Growth velocity decreased to less than +1 SDS during the second year of GH administration but was restored to that observed during the first year of treatment when the dose of GH was increased to 20 IU/m^2/week during the third year. Although predicted height was increased over these 3 years, data on final height are not yet available.

The Dutch Growth Hormone Working Group has now analyzed their data over both 2 and 3 years of treatment.[9,10] They have used several different treatment regimens, with small numbers of patients receiving variable GH dosage. After 3 years of GH administration, they concluded that height prediction was improved very little, if at all.

Albertsson-Wikland[2] treated 24 prepubertal patients for 4 years. The average growth velocity of these children was 8.1, 6.7, 6.0, and 4.9 cm/year during each annual treatment period. Thus, maximum catch-up growth occurred during the first year of therapy and catch-up was no longer evident during the fourth year. Height prediction was increased in these children but, again, final height was not yet available in that report. Height prediction was not increased in 13 pubertal patients who were treated with GH.

Data regarding final height in GH-treated non-GHD children are beginning to trickle into the literature in abstracts and poster presentations. The longest running study is that of Van Vliet et al[11] in San Francisco. Although flawed, this work provides useful information. The patients included were both short and growing at a subnormal rate; in addition, only those who showed a positive response over the first 6 months of therapy received long-term GH. An interim report[12] of the progress of these children suggested that they were continuing to respond and that their predicted mature height was improved. However, a more recent report[13] indicates that, although height prediction improved with GH therapy in 50% of these patients, only 13% (3 of 24) had a significant improvement in actual final height.

More recently, Albertsson-Wikland and Karlberg[14] presented preliminary material on the final height achieved by 33 children treated for variable periods of time with GH 0.1 IU/kg/d. The final height of these children varied from +0.1 to +0.7 SDS when compared with their pretreatment height prediction. A large proportion of those who had received GH over several years failed to improve adult stature.

Summary

What overall conclusions can be drawn at this time?

1. The administration of GH results in a short-term acceleration of growth in a significant proportion of non-GHD children.
2. The positive effect is maximal during the first year of treatment but often wanes with time.
3. Preliminary data on adult height achieved by GH treatment in normal short children is disappointing and suggests that many treated individuals fail to significantly improve adult stature.

Many additional issues remain to be considered. In particular, questions of risk-benefit ratio and cost-effectiveness must be addressed. I hope this presentation fosters further discussion of these areas as well as consideration of the overall effectiveness of GH in non-GHD individuals.

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DISCUSSION I: C & D

C: Efficacy of Growth Hormone Therapy in Patients Without Classically Defined Growth Hormone Deficiency - Raymond Hintz, MD

D: Growth Hormone Is Not Effective in Non-Growth Hormone Deficient Patients - S. Douglas Frasier, MD

Moderated by Jo Anne Brasel, MD

JOHANSON: Would you care to make a remark about what happens to children with constitutional growth delay in terms of their final height?

FRASIER: We have thought and have taught our students, that children with constitutional growth delay, as generally defined, will reach the height expected for their family, albeit they will get there later as they enter puberty late. However, there is an increasing body of information that says this may not be true, and children with constitutional delay may not have progressed as well as we had once thought.

DANIELS: What exactly is meant by "constitutional"?

FRASIER: These are children who are short, growing at a normal velocity, and have delayed skeletal maturation. I don't utilize "constitutional" to talk about children that are growing at subnormal velocity.

MacGILLIVRAY: We do not have a good historical data base which documents the long range outcomes of short children who have what I call "idiopathic growth failure." They differ from children who are constitutionally delayed in that they are growing at an abnormally low velocity. I think the children referred to by Dr. Hintz who had normal growth velocities prior to entering this study are probably a different population.

HINTZ: Yes, they are different. We wanted to see whether children that have higher growth rates when they enter the study responded less well. In fact, that was not true.

MacGILLIVRAY: Children growing at a pathologic rate are not constitutionally delayed. They have a growth disorder. Without an appropriate historical data base, is it fair to assume that achieving predicted adult height is a success?

BAILY: I'm troubled by the idea that we are using growth data from the 1930s. Some ingenuity should be used to figure out noninvasive ways of studying normal growth to establish a baseline and to determine what happens to children who are not going to be treated.

HINTZ: We have many studies of the growth of normal children. What we are proposing is a need for studies documenting the natural history of growth in abnormally short children. With the exception of Turner syndrome, we do not have outcome measures.

ALLEN: Withholding treatment from abnormally short children, while requiring bone age X-rays every 6 months, would be difficult to defend to human subjects committees.

ROOT: The average height of our society has not changed all that much. If you look at the data from the Boston Children's Hospital anthropometic charts (1930s) and compare them to the National Health Statistics study in the mid-1970s, the third- and tenth-percentiles for heights for boys and girls are almost identical to the first decimal place. We are presumably now achieving our growth potential in this population.

Regarding doses of growth hormone, present low-dose treatment is still twice the amount of GH that "in the old days" was effective in making patients with "classical" growth hormone deficiency grow very well.

WEISBARD: If we examine the effect of GH therapy from the perspective of functional *incapacity*, rather than merely a statistically significant deviation from the mean, perhaps we will discover that we are comparing 8 inches in the "classic GH deficiency" instance with 1 or 2 inches in the non-GH deficient child. Could someone clarify what orders of magnitude we are talking about?

FRASIER: For classical GH deficient children, I think the best treatment now available will allow achievement of the height potential expected in that patients' family. For the non-GH-deficient child, we do not know the long-term result.

LANTOS: Would you agree that your best chance for augmenting the height of a short child is to start them younger?

HINTZ: Yes.

LANTOS: Treat them longer?

HINTZ: Yes.

LANTOS: Seven days a week and at higher dose?

FRASIER: Yes, treat them daily, but I am not sure what is meant by "higher dose." The growth hormone log-dose response curve is not linear; there is a limit to the response achieved at the upper end of the dose-response curve, and toxicity can be expected at some higher GH dosage.

ADVERSE EFFECTS OF GROWTH HORMONE TREATMENT

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Introduction

For more than 50 years, growth hormone (GH) has been recognized as a potent chemical messenger, capable of influencing many aspects of metabolism and, of course, stimulating somatic growth. A review of the adverse effects of GH depends on the perspective of the observer. A consideration of childhood acromegaly, in which the previously healthy child is exposed to large quantities of endogenous GH from a pituitary tumor, shows the main adverse effect is gigantism, or excessive growth. In the context of the treatment of short children with GH, however, gigantism is merely an exaggeration of the desired effect. Furthermore, the adverse effects of medications and therapeutic maneuvers have a nasty habit of ambushing us when least expected. Before 1985, only the most farsighted considered the risk that spongiform neuropathies might be transmitted by pituitary GH. Such fears were apparently allayed by experimental studies only to reemerge as cruel reality in a scenario that would credit the best of science fiction writers.[1] GH is currently being given to about 20,000 children in the United States (US) and probably to a smaller total number of patients in the rest of the world. Thus, serious adverse effects occurring with the frequency, for example, of aplastic anemia due to chloramphenicol (approximately 1:10[5]) might well be hidden from us now, only to emerge if GH therapy becomes a much more widely used option. With these cautions, I will review some of the more pressing concerns regarding the adverse effects of therapeutic GH. The listing is not intended to be comprehensive nor, as I have indicated, can our current knowledge be considered an infallible guide to what will be.

The Oncogenic Potential of Growth Hormone

The theoretic possibility that GH could facilitate the development of cancers has long been discussed. GH is known to favor the development of certain mammary tumors in the mouse,[2] perhaps because of its lactotropic effect. The tendency to develop mammary tumors has recently been observed in transgenic mice constitutionally producing large excesses of GH.[3] A cautionary note regarding a possible stimulatory effect in childhood leukemia was sounded as far back as 1977.[4] However, the current high level of concern regarding the development of leukemia in treated children arose in 1987 with the publication of reports by Watanabe and colleagues from Japan[5] indicating that the incidence of leukemia in GH-treated children was much higher than expected on an actuarial basis. In a comprehensive review of the situation as it existed 2 years later, Stahnke and Zeisel[6] analyzed the data on 15 cases worldwide of GH-treated children who had developed leukemia. They noted that 7 children had conditions that might predispose to leukemia and that 2 had been on GH for only a very short time. While most reported cases of leukemia associated with GH therapy have been of the acute lymphoblastic variety, at least 2 cases of acute myeloid leukemia have been reported from Japan.[7,8]

In the US and Canada, a total of 9 cases of leukemia in children currently or recently on GH therapy have been recorded.[9] All but 3 had previously received either radiation or chemotherapy, or had surgery for brain tumors without radiation. The classification of these data remains inexact because of the lack of a central data base to which all such cases can be referred. It is, for example, theoretically possible that the same case, reported to various agencies, has been counted twice in this list. There has been no centralized system for the purpose of confirming such data as the type of leukemia, the temporal relationship to GH therapy, and the eventual outcome. Efforts are now in progress to set up and maintain a central reporting system. In a recent review from the United Kingdom,[10] 16 patients (out of 1,901 treated) developed tumors during or after GH therapy. Four of these had had diagnosed brain tumors before GH therapy was started. Thirteen of these new tumors were intracranial, the others being Hodgkin's lymphoma, osteosarcoma, carcinoma of the colon, and basal cell carcinoma. The authors considered that their survey provided no evidence of an increased risk of malignancy as a result of GH therapy.

The issues raised by the GH/leukemia relationship can be only summarized here. They are:

1. Does GH deficiency (GHD), *per se*, predispose to leukemia?

2. Are children who develop brain tumors intrinsically more likely to develop leukemia?

3. Does chemotherapy, therapeutic irradiation, or a combination of the 2 predispose to leukemia?

4. Does GH increase the incidence of leukemia among patients known to be predisposed to hematologic malignancy, such as those with Fanconi syndrome, and in those patients previously treated for leukemia?

I believe we are a long way from authoritatively answering any of these questions. Nearly all the patients reported as having developed leukemia during or after GH therapy have been GHD. In addition, 1 or 2 cases of leukemia have been reported of developing in GHD, nontumorous children before GH therapy could be started. The annual incidence of leukemia in US children aged 5 to 12 years is about 1:4 x 10.[4] The low number of GHD children and the universality of therapy for GHD children render it unlikely that this question will ever receive an answer.

US data establishing a 3:1 preponderance of brain tumor patients among GH-treated leukemia victims (set against a 3.5:1 preponderance of nontumorous patients in one large survey of GH treatment[11]) strongly suggest that with or without GH treatment, children who have had brain tumors are more likely than the general population to develop leukemia. It will be necessary to obtain good follow-up data on children treated for brain tumors who did not receive GH before the question of whether GH poses a special risk for this population can be addressed.

When the connection between leukemia and GH therapy was first raised, most oncologic and neurosurgical opinion was that neither brain tumors, per se, nor the standard therapies for these disorders were associated with an increased incidence of leukemia. Since then, however, Blatt and colleagues[12] have provided evidence for such a link. Their paper reviews the literature on 10 subjects who developed leukemia after treatment for brain tumors. In an accompanying editorial,[13] Dr. Anna Meadows considers that GH may act as a promoter of expansion of a group of cells that have already sustained a "first event" that set them on the path to malignancy.

Given the pitfalls and limitations of the epidemiologic approach, it is not surprising that experimentalists have tried to discover whether GH might have a direct effect on the transformation of hematologic cells in vitro. Human lymphocytes possess GH receptors and there has been considerable interest in any role that GH might play in modulating these cells' proliferative response to antigen. GH also is capable of influencing the proliferation and differentiation of hematopoietic stem cells,[14] a property that has been used to assess patients' cellular sensitivity to the hormone.[15] Both GH and insulin-like growth factor 1 (IGF-1) have been reported to stimulate the proliferation of cells derived from human hematopoietic malignancies. Physiologic concentrations of both peptides separately increased proliferation of laboratory cell lines derived from human leukemia and lymphoma cells and had the same effect on blast cells freshly obtained from the marrow of children with acute lymphoblastic leukemia and acute myeloid leukemia.[16] The results of this sort of experiment support views such as the one attributed above to Meadows. However, they do not provide any evidence that GH or IGF-1 can induce the transformation of nonmalignant cells into malignant ones. Attempts to show such changes in vitro have been made, but to date none have been successful.

In summary, GH treatment is associated with an increased risk of hematologic malignancy. In the US, this is confined to patients who have been treated for brain tumors, who might well be predisposed to the development of leukemia. In Japan, even children with idiopathic GHD appear to have an increased risk of leukemia when they receive GH. GH might enhance the proliferation of existing clones of transformed cells, but there is no evidence that the transformation event itself can be induced by GH. Much careful epidemiologic and laboratory research remains to be done in this heavily charged area.

Growth Hormone and Metabolic Derangements

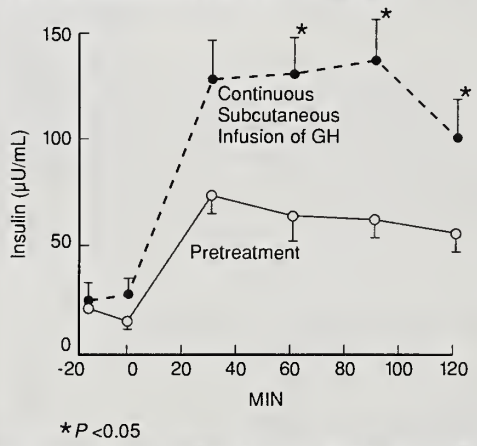
A) Hyperinsulinemia

The relationship between GH and insulin has fascinated diabetologists for many years. Acromegaly is associated with diabetes of the insulin-resistant type and there are reports that glucose tolerance may revert rapidly to normal when a growth hormone-secreting adenoma is resected. In experimental work both insulin-like and anti-insulin actions, probably mediated via different receptors,[17] have been attributed to GH. However, the anti-insulin effect predominates during the long-term administration of exogenous GH. Serum insulin levels rise because GH induces resistance to the glucose-lowering effects of insulin. The reported extent to which exogenous GH induces hyperinsulinemia has varied widely and may depend on such factors as the dose and duration of therapy, the age and body habitus of the recipient, and the mode of administration of the GH. In our study of the effects of continuous low-dose subcutaneous GH infusions in GH deficient children, we observed significant increases in the insulin response to an oral glucose tolerance curve after only 3 days at 0.8 μg/kg/hr[18] (see Figure 1). More recently the Yale group, using a hyperglycemic clamp technique, have demonstrated a sharp increase in insulin resistance when girls with Turner syndrome were started on GH[19] (see Figure 2). Other studies of GH treated children have not demonstrated much in the way of insulin resistance during chronic therapy.

Even if we accept that most children on GH develop a degree of insulin resistance, it is far from clear whether this leads to any harmful consequences. Insulin resistant diabetes as a complication of GH therapy is virtually unknown. Insulin resistance is associated with obesity, hyperlipidemia, atherosclerosis, and ovarian hyperandrogenism. However, none of these conditions are likely to present in the patient population that receives exogenous GH, and they have not been reported as

adverse effects of treatment. Nevertheless, we should remain vigilant, especially as regards any possible delayed incidence of macrovascular disease.

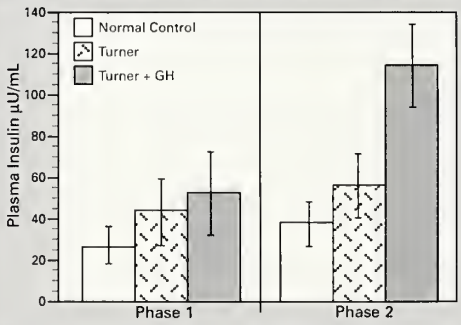
Figure 1: **Effects of Low-Dose Subcutaneous GH on Insulin Response in GHD Children**



*P <0.05

Mean plasma immunoreactive insulin levels from oral glucose tolerance tests performed before and during continuous subcutaneous growth hormone infusion.[18]

Figure 2: **Effects of GH Therapy on Insulin Response in Turner Syndrome Patients**



Mean plasma immunoreactive insulin levels during the Phase 1 and Phase 2 responses to intravenous glucose tolerance tests. The normal subjects were prepubertal girls. Girls with Turner syndrome were studied before and again during daily subcutaneous therapy with growth hormone.[19]

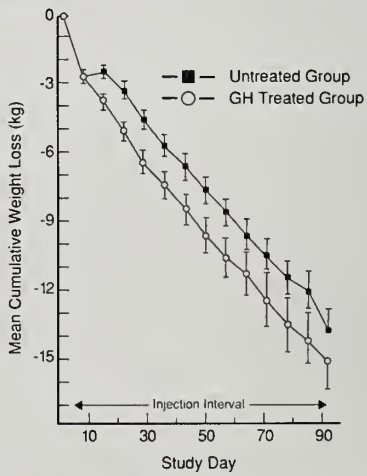
B) Sodium retention

Edema and sodium retention were among the first physiologic consequences of treatment noted by the early GH pioneers. GH-induced sodium retention is dose dependent and often appears to wane in intensity as therapy is continued. The cause is unknown but may reflect an antinatriuretic effect on the renal tubule attributable to GH itself or to IGF-1 or insulin. Mild sodium retention is best detected by careful weighing of the patient. This point is well illustrated in Figure 3 which is taken from Snyder et al[20] and shows parallel declines in mean body weight in obese and nonobese subjects. At every time point during treatment the mean weight is greater in the GH-treated than in the untreated subjects, presumably because the former show a degree of GH-induced salt and water retention. Apart from some discomfort at the lower extremity, and some anxiety when parents observe a symptom known to be associated with serious illness, GH-induced salt and water retention do not pose a clinically significant problem. This statement may, however, lose some validity if GH ever comes into widespread use as an anabolic agent in critical care settings or in the preterm newborn.

C) Increased energy expenditure

One reason for including this subject in a review of the critical adverse effects of GH might be sought in the copyediting practices of some of our leading medical journals, perhaps with the concurrence of investigators who publish therein. The fact that GH induces a marked increase (up to 25%) in resting metabolic rate was first reported by Henneman et al in 1960.[21] At the same time, those authors described a marked fall in appetite which, they said, had originally been observed by Beck et al in the first patient ever to receive human GH.[22] The rise in basal metabolic rate coupled with the fall in appetite and the lipolytic effect of GH all contribute in part to the loss of fat tissue in treated patients, as exemplified by common observation of the results of treatment in severely deficient children.[23] Is this an adverse effect? Certainly so, if the title of a recent *Lancet* paper is to be taken seriously.[24] These authors found a 12% increase in resting energy expenditure after 6 months of GH treatment, together with a considerable decrease in body fat. Even as modified by the terminal interrogative, the title "Treatment of Short Normal Children and Growth Hormone—A Cautionary Tale?" sounds quite provocative. And so it proved, with plenty of attention from the serious press and heightening of general concern about GH.

Figure 3: **Effects of GH Therapy on Sodium Retention**



Mean cumulative weight loss in two groups of adult volunteers on a calorie restricted diet. The initial delay in weight loss observed in the growth hormone-treated group (—○—) relative to the untreated group (—■—) is attributable to sodium and water retention in the former group.

From Snyder et al.[20]

Others have interpreted similar data in a very different light. For example, the article presenting the findings that fat mass was reduced, muscle increased, and heart rate increased was entitled, "Beneficial Effects of Growth Hormone Treatment in GH-Deficient Adults."[25] The statement of Rudman et al that "the effects of 6 months of human growth hormone on lean body mass and adipose tissue mass were equivalent in magnitude to the changes incurred during 10 to 20 years of aging"[26] was soon transformed by the lay press into statements implying that treatment with GH could make individuals look and feel 20 years younger. Like previous authors who had looked at GHD children and adults, these authors found that GH could increase lean body mass (by a mean of 8.8%) and decreased fat mass (by 14.4%). Successive investigators, therefore, going back since the first human use of GH over 30 years ago, agree that GH can profoundly alter the metabolism of both fat and lean tissue.

These changes inevitably accompany somatic growth or any other primary therapeutic action for which GH is given. Perhaps the adverse effect against which we must guard is any tendency to sensationalize observations on the effects of GH and the attendant false hopes and fears that can flow from such handling of our data.

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Table 1: **Review of Literature on Patients With Leukemia Following Treatment of Brain Tumors**[11]

Patient	Age*	Sex	Brain Tumor	Therapy			Interval Between Dx of BT and L	Reference†
				Chemotherapy	Radiotherapy	Leukemia		
1	4.2	M	Astrocytoma, pilocytic††	-	+	ALL	36 mo	4
2	5	M	Glioblastoma multiforme	BCNU V Mtx Dec VP16	+	AMML	15 mo	10
3	6.6	M	Medulloblastoma	CCNU V P	+	Mixed lineage	83 mo	Present case
4	12	M	Malignant ependymoma	-	+	APL	1.5 yr	8
5	18	M	Germ cell tumor (CNS)††		+	ALL	6 yr	3,5
6	30	F	"Malignant tumor" occiput	CCNU VM26	+	APL	38 mo	11
7	39	M	Astrocytoma, grade IV	CCNU VP16 DDMP Dec	+	ANLL	51 mo	12
8	42	F	Anaplastic astrocytoma	CCNU Procarbazine VM26 Adr		AMML RAEB	43 mo	11
9	56	F	Meningioma, angioblastic	CCNU VM26	+	AMML	81 mo	9
10	60	F	Oligodendroglioma	CCNU		AMML	51 mo	9

* Age given in years. months, at time of development of leukemia.
† Reference numbers refer to references given in the paper quoted.
†† GH administered following diagnosis of brain tumor.
NOTE: mo, months; yr, years; BT, brain tumor; L, leukemia; CCNU, lomustine; BCNU, carmustine; V, vincristine; Mtx, methotrexate; Dec, decadron; VP16, etoposide; P, prednisone; VM26, teniposide; DDMP, 2-4diamino-5-4 dichlorophenyl-6-methylpyrimidine; -, not given; ALL, acute lymphocytic leukemia; ANLL, acute nonlymphocytic leukemia; APL, acute promyelocytic leukemia; CNS, central nervous system; AMML, acute myelomonocytic leukemia; RAEB, refractory anemia with excess biasis; Adr, Adriamycin.

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DISCUSSION I: E

E. Adverse Effects of Growth Hormone Treatment - Joseph Gertner, MD

Moderated by Jo Anne Brasel, MD

DANIELS: I was curious to hear about the interaction between sex hormones and growth hormone and the ways in which they may partly affect each other. Does the presence of large doses of growth hormone have a long-term effect on sexual development in puberty or later?

GERTNER: I do not think there is evidence of a long-term effect, and even the effects at the time of treatment are disputed. Charles Brook and collaborators find that puberty is accelerated when growth hormone is given. However, the Collaborative Genentech Study shows no evidence of acceleration of puberty during growth hormone treatment. Sex hormones appear to increase GH secretion at the time of puberty. Yet when one reaches 21 years of age, sex hormones are still made but growth hormone secretion goes down. I do not think there is evidence that growth hormone adversely affects reproductive capacity or sexual function.

FRASIER: Are there clinical circumstances under which you would recommend that growth hormone not be given to a deficient individual because of the possibility that the incidence of leukemia might be increased?

GERTNER: My reading of the Wilkins Society statement and the worldwide literature is that there is an increased incidence of leukemia in patients with a prior brain tumor who have previously had brain tumors and who are now being given growth hormone. This applies whether they had radiation or chemotherapy or even surgery. We have a dilemma and it is not known whether this increased incidence of leukemia is related to or independent of growth hormone therapy.

BRASEL: The Wilkins Drugs and Therapeutic Committee is to meet again in 1993 with cancer and epidemiology experts to reassess the data on this issue. One important question to resolve is, "Is there a subgroup of patients for whom we should recommend no growth hormone treatment under any circumstances?"

FOST: I wanted to raise two questions about efficacy, if I could. This conference is focused obviously on growth hormone treatment for children, but there are other clinical uses. There are recent studies on the effect of growth hormone on aging. Do you think there is anything to that? Is it promising? Is it expanding? And, secondly, what is its effect upon athletes for anabolic purpose and for performance enhancement? Could someone give a brief statement of what they think the state of knowledge is in those areas?

HINTZ: In terms of experiments with growth hormone in aging, there are short-term metabolic effects, some of which may be useful in terms of enhanced protein synthesis. At the other end of the spectrum is the fact that acromegalics do not live forever nor are they particularly strong. None of us has any data about the use of growth hormone therapy in athletes. From what I know about short-term effects in adults, it might be useful in the short term, particularly along with a weight-building program and perhaps androgens. In the long term it is unlikely to be very useful.

LIPPE: There is a third group—the hypopituitary adult.

HINTZ: Right. Well, that is another issue. There you are treating a disease.

JOHANSON: In reference to Dr. Fost's question about athletes or adults, there either has been or will be published in the March issue of *Journal of American Physiology,* a study by Yarashevski and Bier on giving young men growth hormone and also exposing them to training exercises. The growth hormone-treated group showed some changes in metabolic parameters, but did not improve any kind of functional measurements — that is, strength or whatever, in all the things those folks do.

MacGILLIVRAY: I want to ask a question about one of my patients who is a boy of almost 13. He has had total body irradiation and a bone-marrow transplant; he is doing beautifully except he stopped growing after the total body radiation and transplant. He now wants to grow again and to go through puberty. What should I do if I find he is growth hormone-deficient?

GERTNER: Oncologists are adamant in saying, "There is no risk in giving growth hormone." But I do not know how they can be so confident. One can look for clonality in the marrow-derived cells. If someone is going to have a relapse of leukemia, there may already be a clonal element in the present bone marrow. If a relapse were predicted, you would not treat them. I do not know how to respond to your question except to say that we do treat such children with growth hormone if they are deficient.

STANHOPE: I treat them, as well; it is always easy to generalize, but with an individual patient it is much more difficult. With the hematologist or the oncologist, I actually talk to them and tell them what the evidence is before actually letting them make the decision.

UNDERWOOD: One thing I think we are doing right is to focus on these at-risk groups for the possibility of leukemia. I was particularly disturbed by an article in the *Journal of Pediatrics* (1991;119:478-483) that presents the results of a small trial of growth hormone therapy in patients with Down's syndrome who have a known predisposition to leukemia. I think we need to keep focusing on the at-risk groups.

ALLEN: Several of the adverse effects, including psychological effects, of treatment and perhaps even tumor development could possibly be minimized by reducing the duration of exposure to the growth hormone. A French group has reduced exposure time by using high doses of growth hormone for a couple of years. Do you think that is a direction we should be moving in?

GERTNER: I like the idea of short-term trials with high doses, but I do not know the side effects of such a program. I do not know anyone who can tell you that hyperinsulinism of a certain degree for 6 years is worse than hyperinsulinism of a higher degree for 2 years; or that a shorter exposure to a burst of high dose growth hormone is more likely or less likely to cause mitotic disease. There is no data or information to answer those questions.

MACKLIN: One of the hardest things, I find, is to assess risk/benefit ratios. You have now told us about the presumed risks, the perceived risks, the hypothetical risks, the side effects, and the possible long-term but unknown risks. But will the information you provided ultimately help us? Even if we had much better data and much more experience than your report this morning showed, we still might have difficulty with the risk/benefit ratio. So what, then, would you advise, given the uncertainty? Is there a provisional assessment that you can make about these kinds of risks when we are thinking about the risk/benefit ratio?

GERTNER: Well, I will stick my neck out; this is a very, important question. I would say that the risks are extremely small in nondeficient short children, apart from the psychological aspects, which Dr. Stabler may address at some more length. I believe the risk of physical illness and potential harm to children treated with growth hormone is really small.

FRASIER: I do not disagree with Dr. Gertner, but I must add "at presently used doses," because there is this tendency that if a little is good, then more might be better. We need to guard against that.

Session II:

PSYCHOLOGIC AND SOCIAL ISSUES IN GROWTH HORMONE THERAPY

Editor's comments: It is often assumed that a short-statured individual will be socially and emotionally unfulfilled, and concern about psychologic harm is invoked as a primary rationale for treating short stature. Yet, data confirming this assumption and, perhaps more importantly, the efficacy of growth hormone (GH) therapy in alleviating the psychosocial consequences of short stature are scarce. In this session, psychologic risks of short stature and the emotional risks and benefits of its treatment are discussed. The degree to which socioeconomic advantage and gender-related pressures of "heightism" have shaped current allocation of GH is also addressed.

David B. Allen, MD

GENERAL AND SPECIFIC PSYCHOLOGIC CONSEQUENCES OF GROWTH IMPAIRMENT IN CHILDREN AND ADULTS

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Introduction

Growth hormone deficiency (GHD) affects more than somatic growth: those who treat GHD patients are aware of the many social and interpersonal difficulties and problems faced by these individuals. Short stature (SS) has been the focus of explanations for such problems. Only recently has it become clear that lack of stature cannot be solely responsible for the unsatisfying life quality of many GHD patients. This paper documents some of the deficiencies experienced by patients and suggests that an ethical approach to treatment must focus not only on issues of growth and stature but also on issues of social and developmental life quality.

Psychologic Aspects of Height

The principal question governing the therapeutic use of GH is whether the patient qualifies for treatment by virtue of demonstrable absence or insufficiency of GH secretory capacity.[1] Even from this seemingly straightforward viewpoint there is much debate over the criteria for defining GHD. Confounding the issue is a discussion of the concept of "heightism," which alludes to the presumed effect of SS on self-image and hence self-esteem.[2] Arguments are made, as the basis for this belief, that GH treatment be available to non-GHD patients with the expectation that increased growth velocity will improve self-esteem. Much has been written about the adjustment and psychologic functioning of short children,[3] although little has been incorporated into the formulation of ethical guidelines for GH treatment.[4] Allen and Fost[5] present a balanced review of biologic and psychosocial rationales for treating non-GHD "entitled" children under certain circumstances. These authors are concerned that GH therapy be available only to those for whom height is a serious handicap. They insist there is no clear line of demarcation as to what constitutes such a serious handicap, but suggest a height below the 1st percentile. Important to this discussion is the point that height alone is not a reliable predictor of happiness and self-

esteem.[6] Indeed, they suggest that an adult height at the 5th percentile should be considered as a target for GH therapy. Recent behavioral studies of short men suggest that significant psychologic stress is associated with lack of height, even within the range of what is considered "normal-short."[7] Thus, it seems premature to propose absolute height standards for treatment goals, but rather the focus should be on adverse biologic, psychologic, behavioral, and social effects of SS, and how can they be rectified.

Recent Psychologic Research Findings

Several well-controlled studies of GHD children have begun to clarify the nature and extent of the learning difficulties associated with GHD.[8] Siegel[9] has suggested that the academic achievement profiles of GHD children closely resemble those of children with specific learning disabilities and attention deficit disorders. These findings are supported by those of others.[10] Interestingly, a British study examining nonreferred short children (<3rd percentile) found no evidence of school-related difficulties except those explained by socioeconomic status.[11] This finding illuminates the fact that SS, per se, is not correlated with academic difficulties and strengthens the belief that a pituitary disorder is most likely the cause of such problems. Taken together, most recent studies strongly suggest that neuropsychologic functioning is fundamentally impaired in many GHD children. The underlying mechanisms are not clear but the outcome in terms of school performance deficits is well-documented.

Other studies have shown that many GHD children have behavior and social problems.[12] In a recent report from the National Cooperative Growth Study, we found a high incidence of problems related to inhibited-disinhibited behaviors.[13] In a group of patients of various diagnoses about to begin GH therapy, some 27% were reported as having problems ranging from withdrawal and anxiety to distractibility. Others have observed similar traits, although generally in much smaller groups of patients.[14] In considering these findings, it is important to bear in mind that patients with less severe GHD, ie, constitutional SS, as a group tend to demonstrate fewer behavioral deficiencies. Patients with greater GHD, ie, panhypopituitarism, seem to experience more cognitive and behavioral difficulties.[14] This suggests a relationship between psychosocial functioning and degree of endocrine deficiency, a notion not entirely novel in the psychiatric literature.[15]

Comprehensive Care of Short Children

Stature, and our concern with it, is in some ways an obstacle to gaining truly comprehensive care for short children. There is no question that for those children who fit the medical criteria, GH therapy has much to offer as a growth-promoting agent. However, what about the children who do not fit the criteria? And are growth velocity and stature the only focus of treatment? Little is known about the fate of referred-untreated children, since there is no effective follow-up mechanism. However, available studies on children with constitutional delay of growth (so-called normal-short children) suggest they experience a degree of difficulty in their schoolwork and in interpersonal relationships with family and peers.[16] Thus, an argument can be made for considering nonclassic GHD short children as legitimate candidates for treatment since they exhibit many of the characteristics of classic GHD children. Although on standard provocative tests these children may secrete GH at levels above traditional diagnostic criterion, nevertheless they show other signs of neuroendocrine or neuropsychologic dysfunction.[17] If one adopts a comprehensive approach to treatment, these areas of difficulty, ie, inhibited behavior, learning disabilities, difficulty maintaining attention, may all be considered part of the diagnostic syndrome. Therefore, it is possible that patients will present with few or several facets of the syndrome—some with clearly deficient pituitary function and growth delay, others with more subtle signs such as SS and learning disability. If the only criteria applied are biologic measures of GH secretory capacity, many patients will fail detection.

Who Can Assist in Diagnosis and Treatment?

Comprehensive therapy for patients undergoing GH treatment includes attention to behavioral, psychologic, and educational concerns.[18,19] To fully evaluate a patient's needs requires an assessment of cognitive and mental status, social and emotional maturity, educational achievement, and quality of life. Endocrinologists are not trained to do these things, and so consultation from pediatric or clinical child psychologists should be sought. Formal standardized psychometric testing together with individual and family interviews, and school consultation as indicated, will provide much useful data. This comprehensive approach will reveal hidden deficits in many cases, regardless of the presumed etiology of SS.[13] Combining the skills of endocrinologist, psychologist, social worker, and educator permits multiple interventions to occur simultaneously. For example, short children frequently require special educational services at school.[20,21] In many cases these learning problems are overlooked by teachers either because they view the child as generally immature because of stature or because the child is quiet and withdrawn in class, hence never attracting adult attention. Left unattended, these problems gradually impair a child's quality of life and lead to unsatisfactory social and vocational adjustment in adulthood.[22] Recognizing the potential for such problems and initiating early intervention contributes greatly to improved social functioning and better overall treatment outcome.[18]

Growth Hormone Patients as Adults

The need for GH persists through life, albeit in diminishing levels.[23] Treatment of GHD patients with GH replacement therapy is usually discontinued when epiphyseal fusion occurs

and/or stature approaches normalcy.[1] Recent research implies that this approach may end treatment prematurely and leave GHD patients with an unacceptable quality of life.[24] GHD adults fare poorly in the educational, vocational, and social domains.[25] They live with their parents longer,[26] marry less frequently,[27] and achieve little academic success[22] compared with their normal peers. Importantly, GHD adults report experiencing a diminished quality of life, they particularly lack energy, and experience social isolation.

Although much has been written about the presumed effects of lack of stature on self-esteem, there is little empiric evidence for such claims. Martel and Biller[6] found short males reported being stigmatized for their stature and experienced increased anxiety in many social situations. Hensley[7] correlated height, gender, and self-esteem in a group of 210 undergraduates. He found no clear relationship between SS and low self-esteem. We recently compared 25 adult hypopituitary patients with an age-, sex-, and education-matched group of normal short individuals.[28] Psychometric tests showed the hypopituitary patients to be more introverted, less open, and less assertive than normals. Their physiologic response to behavioral stress was also much less marked than normals, suggesting their social behavior is as much influenced by endocrine deficiencies as by height. McGauley[29] tested the quality of life of 24 GHD adults before initiating GH treatment in a double-blind, placebo-controlled study. After a 6-month trial, GH-treated individuals reported significant increases in factors associated with improved quality of life, increased energy, and less perceived illness. Other studies have shown that GH treatment given to GHD adults increases certain cognitive functions such as short-term memory.[30] Salomon et al[31] demonstrated the metabolic effect of GH replacement in GHD adults, noting that increases in lean body mass and reduction in fat mass occurred.[31]

Evidence is mounting that supports the view that GHD adults on continued GH treatment benefit in many ways unrelated to their height status. Many of these individuals are living unsatisfying and unproductive lives. These deficiencies in life quality cannot be attributed solely to the deleterious effects of SS and inappropriate socialization during childhood. Long-term comprehensive treatment utilizing hormone supplementation, vocational rehabilitation, and psychologic counseling is necessary to ameliorate the myriad difficulties faced by GHD adults.

Summary

GHD is a lifelong condition that requires treatment consistent with specific individual needs on a continuing basis. GHD is not a unitary condition affecting only growth rate and stature. Beginning in childhood it is known that GHD individuals experience a number of learning and behavioral difficulties not associated with growth rate or stature.[8] Unfortunately, treatment is directed only toward the problems associated with growth. Moreover, this treatment regimen usually ceases when epiphyseal fusion occurs, thus never addressing many important symptoms nor considering a patient's long-term needs. These patients grow up to be adults with poor educational preparation, few friends, and inadequate job skills. In addition, because of their endocrine deficiencies, GHD adults may lack the assertiveness and competitive drive necessary for success in the modern workplace. Proper treatment of these problems requires a comprehensive, multidisciplinary approach.[19] Through such methods, we may expect more satisfactory treatment outcomes for these patients and their quality of life.

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SHORT STATURE, STIGMA, AND BEHAVIORAL ADJUSTMENT

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Introduction

Whether growth hormone (GH) therapy enhances self-esteem and behavioral adjustment is at the heart of the current debate about treating short children with GH.[1] The assumptions underlying the rationale for treatment appear to be that: (1) short stature (SS) is a stigma that can compromise behavioral development; and (2) improved growth rate and/or increased stature relative to peers is likely to result in improved self-esteem and behavioral adjustment in the patient. The few studies of self-esteem in children treated for SS provide contradictory evidence of improvements,[2] and the larger literature on stigma and self-esteem indicates that stigmatization does not automatically lead to poorer self-esteem and adjustment.[3] This report will review available data on self-esteem in children treated for SS and the likely connections between stigma and self-esteem that are seen in the social psychology literature. The present focus is limited to normally proportioned SS individuals for whom the principal observable difference is one of height deficit relative to the individual's age and sex peers. The reader is referred to other sources[2,4,5] for reviews of methodologic problems such as lack of control subjects, small samples, varying measurement strategies, and pooled diagnostic groups that have complicated the interpretation of existing data on clinical samples.

Definitions

Self-esteem refers to a person's global sense of self-worth or satisfaction with one's self.[6,7] Stigma is a characteristic that engenders discriminatory behavior on the part of others. Stigmatization refers to the sociopsychologic process of holding negative opinions of others based upon the belief that they are different from the observer's reference group. Typically, stigmatization involves formulating judgments about other people based upon attributes they are perceived to possess and acting upon those judgments in a way that undesirably restricts their opportunities for growth and development. It is closely related to prejudice, discrimination, and negative stereotyping. The process has been studied in such diverse groups as blacks,[8,9] women,[10,11] the obese,[12] the mentally ill,[13,14] the physically disabled,[15] persons judged to be unattractive,[16] and short men.[17]

SS is a *relative* concept, and invariable definitions of who is "short" are not possible. In practical terms, this means that there will always be short individuals even though a short person in one population may have the height of a tall person in a different population. Given the ubiquitous nature of SS, what can be said about the personal and psychosocial correlates of SS?

Height and Social Interactions

Extreme SS is a handicapping disadvantage, especially in negotiating a physical world designed for average-statured individuals. Physical size and height, in particular, also play a role in shaping interpersonal interactions. Height is positively correlated in adults with perceived levels of authority[18]; potential threat[19]; social status[20]; salary, promotions, and hiring[21]; and interpersonal spacing.[22,23] Outcome studies of groups of former GH recipients have associated low rates of employment and marriage with SS.[24]

Clinical studies of GH-deficient (GHD) children have noted a tendency for these children to be juvenilized by other people.[4,25,26] Juvenilization results from the incorrect belief that, for example, a 10-year-old child with the height age of 6 years *really is 6 years old*. Lack of pubertal development is likely to compound the misperception. Juvenilization is particularly common during interactions with strangers, but parents and health-care professionals are not immune from the natural tendency to "believe one's eyes."[27] A common example, which most SS teenagers can report, occurs when the server in a restaurant automatically hands the teenager a child's menu, unwittingly restricting the opportunities of the teenager. GHD young adults are clearly aware of having been treated younger than their chronologic age.[27] The impact of this phenomenon on psychosocial development has not been systematically studied beyond documenting its occurrence.

Juvenilization has been cited as a major factor in the adjustment difficulties of short children. While no clear pattern of adjustment problems has been identified, behavioral immaturity, social withdrawal, depressive symptoms, and low self-esteem have been suggested as outcomes of juvenilization in various clinical samples of SS children.[2] However, the extent to which

the adjustment difficulties seen in clinical syndromes can be attributed to the process of stigmatization rather than syndrome-related psychophysiologic features has been questioned. Turner syndrome (TS) girls have low self-esteem compared with test norms and more adjustment problems than a matched sample of girls with familial SS.[28,29] TS girls also showed poorer skills decoding the affective meaning of facial expressions. Thus, specific neuropsychologic differences between TS and non-TS girls may be more important than SS in explaining the observed differences in adjustment. Similarly, school difficulties shown by some GHD children may be related more to atypicalities in their intellectual and attentional skills than to psychosocial reactions to SS.[30] Low rates of dating, marriage, and sexual activity reported for young adult male hypopituitary patients also may be related to both the stigma of SS and neuroendocrine deficits.[31-33]

The fact that some but not all SS patients evidence adjustment difficulties argues that SS, per se, cannot completely explain the adjustment difficulties seen in clinical groups of SS children. A better understanding of SS children with successful behavioral adjustment, as well as multivariate comparisons of clinical samples with matched normal control subjects, is needed to clarify these questions.

The Short Stature Stereotype

Both adults[17] and children[34,35] ascribe more negative attributes to short persons than to tall persons. For example, typical attributes assigned by 5- to 13-year-old schoolchildren to the shortest of 3 human silhouettes were "weak," "scared," "follower," "no friends," and "unsuccessful." In contrast, the same group of 229 children assigned "strong," "leader," "brave," "smart," and "awesome" to the tallest silhouette.[36] The attributions of the youngest children (5 to 7 years) did not differ from those of the oldest group (11 to 13 years) even though the youngest children had a much less accurate knowledge of their own height and relative height position among their peers.[37] Undergraduates of both sexes rate short men more negatively than tall men. This effect was more pronounced for men who were themselves short (62 inches to 65.5 inches) than for men who were average (68 inches to 70.5 inches) or tall (72 inches to 76 inches).[17] Similar ratings of men were given by undergraduate women. Also, undergraduate men (especially short men)[17] tended to overestimate their own height.

There also appears to be a sex difference in the way males and female value their body and in the value that Western society places on shortness in men and women. In general, men form a global evaluation of their entire physique in which larger is better (except obesity). Women develop a more detailed evaluation based upon various body parts; thus, smaller (except breasts) is more highly rated.[38] In terms of society's expectations, small women are generally viewed as being cute or petite, whereas short men are seen as less competent, withdrawn, and less desirable than taller men as dating partners.[17] Mothers[39] and teachers[40] of preschoolers rate taller, more muscular children as more competent and socially influential. The effect seems to be more pronounced for boys than girls and may help explain why fewer girls are treated for SS. These and similar data[38] suggest that, all other things being equal, SS tends to be associated in the minds of others with less desirable personal attributes, especially for males. Furthermore, this perception is established by middle childhood and continues into adulthood.

Self-Image, Self-Esteem, and Behavioral Adjustment

Self-image (one's multidimensional representation of oneself) is associated with one's self-evaluation of personal worth (self-esteem).[38,41] Several theories about the development of self-concept predict poorer self-esteem and adjustment difficulties as an outcome of exposure to social stigma generally[42,43] and the stigma related to SS particularly.[17,44] The data are not clear, however, whether social stigma *automatically* results in poor self-esteem in the general population[3] or for SS individuals.[2,45]

Early work[46] establishing a positive correlation between satisfaction with one's body and high self-esteem has been replicated in various ways.[47-49] However, this relationship is not necessarily a causal one. The importance to an individual of any particular dimension of self-image (eg, physique, achievement, social skills) appears to have an important influence on the dimension's association with ratings of global self-esteem.[3,50] For example, some children with high self-esteem concurrently rate their physical appearance, academic competence, and/or behavioral conduct poorly. The importance of the negatively rated dimensions appears to be "discounted" relative to children's feelings of global self-worth.[50] Focusing on one's strengths may provide an avenue to high self-esteem in the face of social stigmatization. Consequently, it appears possible for children to have a poor image of their physique due to SS while maintaining high levels of overall self-esteem and self-worth.[2] This phenomenon provides a rationale for psychologic intervention to manage an insult due to stigmatization.

A further complication in interpreting the relationship between a negative stereotype of SS and self-esteem can be inferred from studies of self-esteem and stigmatization due to race[51] and sex[52] that found no decrement in self-esteem following a negative social appraisal when the source of the appraisal could be identified as prejudiced. The overall self-esteem of a SS child, therefore, might *not* be adversely affected when the child perceives the source of the stigmatization as prejudiced against or unfair treatment of himself/herself.

A third complicating factor for understanding the impact of stigmatization due to SS on self-esteem derives from the importance of knowing to which group the social comparison is being made. Specifically, insults to the self-esteem of short children may not be potent if the child identifies primarily with other short children. Mainstreamed mentally retarded (MR) children rate their scholastic competence as highly as classmates

with normal intelligence while mainstreamed students with learning disabilities (LDs) but normal intelligence rate themselves more poorly than regular students.[7] Examination of the primary reference group for the MR and LD children showed that the MR children routinely compared themselves to other MR children while LD children compared themselves to non-LD children. Thus, the stereotype associated with SS may not contribute to negative self-esteem when the SS child perceives his/her competence in a specific area as being better than the competence of other SS children.

Treatment and Self-Esteem

The available data provide information on the behavioral correlates of treatment rather than demonstrations of treatment effects. There have been no placebo-controlled evaluations of the behavioral effects of GH treatment. The challenges of conducting such a study are significant.[5] Available reports involve patients treated with pituitary-derived GH and with treatment schedules and expectations that were quite different from the options made possible by biosynthetic GH. Consequently, the effects of modern GH therapy on behavioral functioning have yet to be demonstrated.

Early clinical reports suggested that GH treatment was associated with a "readjustment syndrome" in which patients were forced to reexamine their own behavioral expectations as the expectations of other people changed.[53] Increased depression, unrealistic treatment expectations, and behavioral inhibition have been reported in patients receiving intermittent[54] and continuous[55] GH treatment. About half of such children also exhibited low self-esteem. Parents, as well as children, have unrealistic expectations of the effect of GH treatment.[56]

Only 1 of 4 published prospective studies[5] using well-standardized behavioral measures assessed self-esteem. Siegel[30] found no differences in the self-esteem of GHD children who were underachieving in school compared with those who were achieving adequately. Contradictory comparisons of self-esteem in GHD and control patients have been reported at professional meetings.[57,58] Rosenfeld et al[45] presented data on the effect of a brief course of testosterone on the self-esteem and social activities of teenage boys with constitutionally delayed growth and puberty. Teenagers showed poor self-esteem ratings at baseline and improvement in self-esteem 1 year later, regardless of whether they received the testosterone treatment. However, only the treated group reported increases in the frequency of socializing at the 1-year mark.

Summary

Several important links are missing in our understanding of the effect of the stigmatization on the psychologic and social development of SS children. As noted above, there is ample reason to believe that SS is associated with a negative stereotype, at least in males, and that stature plays a subtle but important role in determining how one is treated by other people. However, the relationship between these 2 phenomena and the self-esteem and adjustment of SS individuals has yet to be clearly drawn. Some SS children have self-esteem and/or adjustment problems while others do not. How are the poorly adjusted children different from the well-adjusted ones? The existing studies of stigma present cross-sectional data on *groups* of stigmatized persons rather than prospective analyses of the course of development of stigmatized *individuals*. We, therefore, know little about how a SS child develops a reference group for comparison, or under what circumstances a SS child can devalue the stigma of SS and focus upon his/her strengths.

There have been no comparisons of clinical and nonclinical samples of SS children. It is not know, therefore, if the adjustment and self-esteem characteristics of the 2 groups are the same or different. Perhaps the SS cases that come to medical clinics are more likely to be experiencing behavioral and emotional difficulties.

Lastly, psychosocial phenomena are inherently multivariate. At the very least, sets of physiologic and psychosocial factors interact to produce a given behavioral outcome. Focusing predominantly on 1 or 2 specific factors is likely to produce an understanding of only limited utility.

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DISCUSSION II: A & B

A. General and Specific Psychologic Consequences of Growth Impairment in Children and Adults - Brian Stabler, PhD

B. Short Stature, Stigma, and Behavioral Adjustment - Richard Clopper, ScD

Moderated by Louis Underwood, MD

CALLAHAN: It seems to me that the older one gets, the less important stature is. By the time one is 50 or so, people do not seem so big. The big people seem to be diminished. It would be interesting to do a longitudinal study to see how perceptions of height change over the course of a lifetime.

CLOPPER: That study has not been done; however, it seems that as people grow older, they successfully adapt to the insults that come with being short or tall or colorblind. I think that the aging process has the effect of smoothing over many of these social interactions—in helping individuals to turn a situation to their advantage.

STABLER: Individuals who do not have neuroendocrine impairment have many things going for them that allow them to compensate. In my experience, individuals who are not endocrinologically compromised can adapt to almost anything, through acceptance, modification of their behavior, and development of personal style. The condition, and adaptation to it, becomes part of their persona.

LANTOS: Toward the end of your talk, Brian, you indicated that there is a relationship between depression, other psychosocial problems, poor school performance, and short stature. We know from existing study data that certain extreme psychological problems can lead to neuroendocrine problems which, in turn, lead to short stature. When we look at people who are short and have low growth hormone levels and poor school performance, we are accustomed to deducing that the low growth hormone level is the cause and the poor school performance is the effect. But is it possible that the depression is the primary factor in both the growth hormone level and the poor school performance?

STABLER: Yes, I think such a biobehavioral connection is entirely possible. "Growth" is a term that we use in referring to the vast range of all types of growth, including our emotional growth. "Development" however, is a more

STABLER: germane and meaningful term that perhaps more accurately connotes the complexities we are addressing here.

HINTZ: What is more effective for treating these children, psychotherapy or growth hormone therapy?

STABLER: I am not sure that I know, but you would never want to treat anyone with growth hormone without some type of counseling or psychotherapy. I think this work can be done by nurses, social workers, school counselors, or school nurses to mention a few resources. The key is to build ego strength in the child as growth is accelerated.

GROWTH HORMONE TREATMENT: DOES ASCERTAINMENT BIAS DETERMINE TREATMENT PRACTICES?

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Introduction

This report will focus on the question, "Does ascertainment bias determine the patient population currently being treated with growth hormone (GH) in the United States (US)?" As the basis for our analysis we will use the data base provided by the National Cooperative Growth Study (NCGS), a postmarketing surveillance program established by Genentech, Inc at the time Protropin® was introduced in October 1985. Currently, over 12,000 children treated with GH have been enrolled in this program. This sample is estimated to represent more than 50% of patients who have ever been treated with GH in the US and more than 70% of those treated with biosynthetic GH; it is the largest collection of data ever assembled to assess GH treatment practices. It includes data on a cohort of patients previously treated with pituitary GH whose treatment was stopped when pituitary GH was withdrawn from the market due to potential contamination with the agent that causes Creutzfeldt-Jakob disease; a cohort with no prior treatment who enrolled between 1985 and 1987; and another cohort with no prior treatment who enrolled from 1988 to the present. These cohorts will be referred to as groups 1, 2, and 3, respectively. Some of the data from the first 2 cohorts have been previously reported[1] and the current data have been submitted in abstract form.[2] The data in this report represent the diagnostic categories and demographics of all patients enrolled in the study, regardless of whether they have stopped receiving treatment. The analysis demonstrates that while diagnostic criteria may be changing, treatment is still largely restricted to white males, while females and blacks continue to be underrepresented.

Methods

Over 350 pediatric endocrine centers currently participate in NCGS. The pediatric endocrinologist or designated staff member fills out a 2-page enrollment form designed by the NCGS coordinating endocrinologists. Patient data are coded by initials and date of birth, and patient (family) permission to participate is obtained whenever required by the local institutional review board (IRB).

Enrollment data include: gender; race/ethnic origin; height at diagnosis (if patient is in group 1) or at enrollment (if patient is

in group 2 or 3); GH test results; and clinical diagnosis. The diagnosis of GH deficiency (GHD) is subdivided into idiopathic GHD (IGHD) and organic GHD (which is further subdivided into craniopharyngioma, other central nervous system (CNS) tumors, irradiation, infection, trauma, CNS defects, histiocytosis X); septo-optic dysplasia (SOD) is listed separately. Patients enrolled with a medical condition not defined as GHD were classified either by their identified diagnosis, ie, leukemia or a chromosomal defect such as Turner syndrome (TS), or placed in a separate category called "Other." Enrollment information also included associated disorders such as hypoglycemia.

Height standard deviation scores (SDSs) for patients were calculated using mean heights and standard deviations (SD) for normal subjects derived from the National Center for Health Statistics[3] using the following formula: SDS = (height – mean height for normal subjects of the same sex at given age)/SD of height for normal subjects of the same sex at this age. In the GHD groups, the peak GH concentrations were not normally distributed and were truncated (since we arbitrarily excluded patients from these groups with values in excess of 10 ng/mL) so that medians were computed and nonparametric tests were used to test for significance among groups. Data entry and management were performed by Biometric Research Institute, Inc., in Arlington, Virginia. Data were analyzed by the Biostatistics Department at Genentech, Inc.

Results

Table 1 shows the demographic characteristics of all 12,046 patients by sex, race/ethnic origin, diagnostic category, and history of previous GH treatment. Overall, males outnumber females by a 2:1 ratio. When the TS category is subtracted from the female group, females are outnumbered by a ratio of 2.6:1. Whites account for almost 87% of treated children, with blacks representing 5%, and Hispanics, Asians, and Other constituting the remaining 8%. The actual percentage of blacks, 5.3%, is only one third of what might be expected given that it is estimated that 15.5% of the US population 19 years of age or younger is black.[4]

Table 2 subdivides the different diagnostic categories by sex. The male to female ratio of the IGHD group is 2.9:1, which is the same ratio as in the Other group, 2.9:1. While overall the organic GHD group was less skewed in sex distribution (1.7:1), only the smaller groups of CNS defects, histiocytosis X, and SOD approached a 1:1 sex ratio.

Height SDSs were examined for the IGHD, organic GHD, SOD, and Other groups. For both the previously treated patients (group 1) and the never-treated patients (groups 2 and 3), there were significant differences between males and females, with females being statistically shorter than males in the IGHD and Other groups. There were no significant differences in height SDS between males and females in the organic GHD and SOD groups. When whites were compared with blacks, there were no significant differences in height SDS in group 1 in any of the diagnostic categories. However, in groups 2 and 3 blacks were shorter than whites in the IGHD and Other groups. In addition, while we note that the actual height SDS at which patients with IGHD were being enrolled has become less negative (that is, the patients are less short relative to children of the same age and sex), since 1988 the overall sex and racial differences have remained.

The median maximum GH concentrations achieved during diagnostic testing was evaluated over the course of this study. For group 1 patients (who had been previously treated with GH prior to initial enrollment), there was a significant sex and racial difference in the concentrations, with median maximum GH concentrations being lower for females than for males and lower for black males than for white males. The maximum GH concentration was noted to increase over time for patients enrolled with no previous treatment, so that the difference in median maximum GH concentration between males and females was not as significant, but both black males and females had lower values than white males and females.

Discussion and Conclusions

The 12,046 patients reported in this study represent a majority of the children who have been treated with GH in the US since 1985. Thus, an analysis of their demographics provides a basis for the discussion of treatment access. We will focus on several aspects of the question of access and hope that additional insights and perspectives will emerge from the discussion.

Table 1: **Genentech National Cooperative Growth Study Demographics of All Participants**

n=12,046*

1985-1991

Demographics	n	Percent
Sex		
Male	7,939	65.9
Female	4,107	34.1
Race/Ethnic Origin		
White	10,389	86.25
Black	639	5.3
Hispanic	299	2.5
Asian	232	1.9
Other	429	3.6
Etiology		
Idiopathic GHD	5,051	41.95
Organic GHD	1,303	10.8
Septo-optic dysplasia	281	2.3
Turner syndrome	1,110	9.2
Other	4,243	35.2
Previous Treatment		
Yes	2,018	16.8
No	9,970	82.8

GHD, growth hormone deficiency.
* Small differences in subtotal reflect missing data.

Table 2: **Genentech National Cooperative Group Study Participant Etiology by Sex**

Etiology	Sex				Ratio
	Male		Female		
	n	Percent	n	Percent	Male:Female
Idiopathic GHD	3,752	74.3	1,299	25.7	2.9:1
Organic GHD	813	62.4	490	37.6	1.7:1
Infection	11		0		11:0
Craniopharyngioma	251		148		1.7:1
CNS Tumor	315		191		1.6:1
Trauma	49		24		2.0:1
Irradiation only	90		51		1.8:1
CNS defects	82		61		1.3:1
Histiocytosis X	15		15		1:1
Septo-optic dysplasia	165	58.7	116	41.3	1.4:1
Turner syndrome			1,110		
Other	3,163	74.5	1,080	25.5	2.9:1
Total	7,893	65.8	4,095	34.2	1.9:1

CNS, central nervous system
GHD, growth hormone deficiency

The first is the issue of the sex difference found in the IGHD group. The predominance of males is not a finding new to this study, having been previously reviewed by us[1] and reported in virtually all studies of GHD around the world, including the surveillance study parallel to NCGS currently being conducted in Europe.[5] However, in almost all cases, the diagnosis is made at a tertiary center and therefore is largely dependent on the demographics of the patients referred for evaluation. Thus, one has to ask if the predominance of males is due solely to biologic differences or whether social factors play a role. That there are biologic differences which account for some degree of male predominance is suggested by the higher incidence of breech delivery and/or perinatal asphyxia in male infants, and the reports of these complications occurring frequently in males with GHD. Other biologic or suggestive causative factors have not emerged. Conversely, the first report of GHD detected by population screening of schoolchildren (using a height SDS of –2.5 for initial ascertainment) noted that "none of the children with previously diagnosed GHD were girls, although 5 of the 9 children found with GHD during the study were girls."[6] This group later went on to study much larger numbers of schoolchildren and to note a male to female ratio of 1.5:1,[7] which is not nearly as great as the 2.9:1 ratio in this data base. In addition, when one looks at the height SDS of the children detected by population screening, there are no significant differences between the males and females. Finally, our initial examination of the NCGS data base in October 1987 noted a lesser sex ratio (2.5:1) than we find now. All these data suggest that as awareness of available treatment for GHD increases, there is an even greater tendency to refer or test males as compared with females. Our data show the same 2.9:1 sex ratio in the Other group, comprised largely of children who do not have classic GHD, to further support the hypothesis that referral may be biased toward males.

While it is beyond the scope of this paper to provide an in-depth discussion of the possible reasons for sex differences in the organic GHD patients, we will include this group in the discussion of a second issue, namely, the height SDS at which the diagnosis of GHD is made. Females are statistically shorter than males at the time the diagnosis of IGHD is made, but not at the time the diagnosis of organic GHD is made. When height SDS data were analyzed over the years of this study for the IGHD group, it was noted that the SDS at the time of entry is increasing for both males and females, but the differences between them remain. Since we are unable to develop a biologically based hypothesis for the height differences occurring between males and females with IGHD as we did in the organic GHD groups, we can only conclude that short stature in the otherwise healthy child is perceived differently by the family and/or the physician depending on the sex of the child. Females who are short may be perceived as "cute" but not pathologically short until their SDSs are more adversely affected than those of males.

A third, interrelated, issue is the absolute peak GH concentration reported for the patients diagnosed as having IGHD. Notwithstanding the fact that these measurements were done in numerous laboratories by many methods, there were statistically significant differences in the concentrations for males and females, with females having lower values. This tends to support the finding that not only are females shorter at the time of diagnosis than males, but they also have a more severe degree of GHD.

Finally, we will briefly discuss the racial demographics of our patient population as it pertains to whites and blacks (since the number of patients in the other racial/ethnic categories is currently too small to assess meaningfully). We are not aware of any studies in the literature that discuss the prevalence of GHD

among blacks. Thus, the fact that we are considering blacks to be underrepresented in NCGS is based entirely on the 15.5% figure that has been reported as the percentage of blacks in the US 19 years of age or younger.[4] The data for the patients in NCGS, however, can be assessed independently of the issue of proportionate representation. We note that among the IGHD group, black males overall are shorter than white males, and black females are shorter than white females. When mean maximum GH concentrations were assessed, blacks had significantly lower concentrations than whites. Finally, a disproportionate number of blacks in NCGS had the concomitant pretreatment diagnosis of hypoglycemia as compared with whites. Taken together, these data suggest that referral for evaluation may be delayed in blacks unless there is a medical condition, such as hypoglycemia, that prompts ascertainment.

We have not discussed whether patients actually being treated with GH represent an unbiased sample of the patients referred for evaluation or even of those for whom treatment has been prescribed. That dimension includes not only the economic aspects of treatment access but also the medical criteria used by the physician to initiate an evaluation and the medical and social criteria used to recommend therapy. These questions can be answered only by prospective data collection.

In conclusion, we feel that the NCGS data strongly suggest that nonbiologic ascertainment bias has played and continues to play a role in determining the demographics of patients being treated with GH. While one could take the position that, as a part of this bias, there are groups of children for whom the treatment criteria might be arguable, we must strongly stress that clearly there are groups of children who are not being treated, or are not being treated in a timely fashion. The ethical and social conclusions that emerge from this conference must embrace this concern.

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DISCUSSION II: C

C. Growth Hormone Treatment: Does Ascertainment Bias Determine Treatment Practice? - Barbara Lippe, MD

Moderated by Louis Underwood, MD

UNDERWOOD: I guess we can conclude that ascertainment bias is not primarily the fault of the pediatric endocrinologist.

LIPPE: That is my conclusion.

BAILY: There is an underlying implication that somehow it is bad that women are shorter. But it seems to me that if you had a treatment to make people shorter, interested girls would overwhelmingly outnumber boys. The fact is that it is much more of a social handicap for boys to be short, and therefore, not surprising that short girls are not often identified or selected for treatment.

LIPPE: I would differ with you because black children and girls with brain tumors are *also* not being identified. Secondly, I do not think it is fair to say that just because people have not paid as much attention to girls and blacks that they should be denied a look. We used to treat tall girls to make them shorter, but they are not asking for that treatment anymore.

HINTZ: If your hypothesis is correct, Barbara, there should be a large number of untreated adult females. Has anybody looked?

LIPPE: I think not.

BAILY: The preceding 2 speakers were talking about the bad effects of being short from a psychological and psychosocial point of view. If, in fact, this is the main benefit of treatment and short stature is less of a social handicap for girls, it is not surprising that fewer girls are identified and referred for evaluation. You also seem to be suggesting that there are medical implications associated with short stature as well, so that if I have a short daughter, I ought to bring her in even though I am not bothered by her shortness. Can you please clarify this for me?

LIPPE: The message is that we ought to look at individuals equally first and make the judgments later. I do not think we should deny them access first.

CHARO: Based upon information provided in the first presentation, I understood that specific objective problems associated with growth hormone deficiency are *not* the result of the way the world interacts with the person with the deficiency. I thought that was the point of the comments about attention deficit, hyperkinetic activity, and similar conditions. Thus, it seems we are considering two categories of patients: those who need to be identified because they have a condition that should be addressed with some kind of medical treatment, and those for whom stature is a cosmetic issue akin to having a complexion blemish.

The fact that women are shorter, in general, may be a very significant factor in explaining the phenomenon of gender relation. It would seem dangerous to dismiss the need to identify girls who are shorter than their genetic potential as not being in need of treatment because the *cosmetic* impact is not perceived as a significant disability.

STABLER: Part of the problem may be that many pediatricians have a perspective that contributes to referral bias. Many pediatricians have difficulty arriving at the decision to refer a patient to the pediatric endocrinologist. Given that bias, there is reason to suspect that pediatricians may be biased in respect to gender, too.

LANTOS: Your presentation seems to assert that short women are underrepresented rather than short men being overrepresented, and that ascertainment of growth hormone deficiency and the provision of treatment is a good thing. I am not sure I am ready to go along with that. Consider the historical treatment of tonsillar irradiation in Chicago as another therapy that was subject to class bias when it was first used. A presentation like yours would have shown that blacks and poor people were being discriminated *against*, when, in fact, these people were favored by not receiving a treatment that was later determined to be linked to the development of thyroid cancer. You could argue that middle class white males are being tortured with a shot a day for 5 years that offers them little benefit, all because their parents believe that the therapy is good for them.

LIPPE: Well, *you* could argue that! (laughter)

Session III:

CONCEPTUAL AND ETHICAL ISSUES IN ENTITLEMENT TO GROWTH HORMONE TREATMENT

Editor's comments: Traditional clinical endocrinology is firmly rooted in a disease-oriented model of medicine, ie, the replacement of deficient hormones and suppression of hormonal excess. With the advent of growth hormone (GH) treatment of non-GH-deficient children (eg, Turner syndrome), GH enhancement therapy has been added to GH replacement therapy. Is short stature now considered a "disease?" Is the disease label still relevant to the issue of entitlement to GH therapy? Is GH enhancement therapy a justifiable medical endeavor? These questions, addressed in this session, illustrate the complex ethical dilemmas that emerge from expanding GH efficacy and availability.

David B. Allen, MD

THEORETICAL AND POLICY DEBATES OVER THE STATUS OF SHORT STATURE AS A DISEASE

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Introduction

Is short stature (SS) a disease, and does its designation as such really matter? The debate over these questions can be carried out at 3 levels, which I will label the "clinical," the "policy," and the "theoretical," respectively.

The Clinical Level

By "clinical," I refer to the debate among clinicians and clinical scientists over the physical and psychologic risks and benefits of human growth hormone (GH), administered both to GH-deficient (GHD) and to normally short, non-GHD children. I also include in this category the technical disputes over how GHD can be measured, and the difficulty of agreeing on a cutoff point for defining it.

The Policy Level

I will use the term "policy" as shorthand for a number of social, moral, economic, and political issues that play a role in determining the proper course for public policy on the allocation of GH: its cost, its effect on other elements of health care, and questions of entitlement and justice.

The Theoretical Level

By "theoretical" I refer to questions about the status of GHD and SS as diseases, when we consider these questions in abstraction and divorced from policy debates — assuming that one can do so.

I will have little to say about the clinical issues. Their resolution does, however, have important bearing on the other 2 categories of questions. They become most interesting only if GHD can be well-defined, and only if GH provides more benefit than risk for normally short as well as for GHD children. If these claims are untrue, then the policy and theoretical issues are relatively moot.

My aim in this paper is to sketch some of the logical relationships that hold among these levels of debate. Drawing on the insights of some philosophical colleagues, I will argue that the policy questions are not entirely independent of the theoretical ones, although the political process might ignore these entailments. This directs us to look to theoretical accounts of the concept of disease to help in settling our policy disputes. However, I will suggest that the issues of GHD and SS may be especially difficult cases for the best of these accounts, and that we may be frustrated in looking to them for guidance.

Is the Policy Level Sufficient?

Assuming the outcomes stated above in the clinical debates, do we need to ask whether SS is really a disease, ie, to enter the theoretical debate at all? Could we not determine the issue like any other question of public policy, referring in the main to the positive and negative consequences of providing GH to normally short children? Indeed, much of the debate so far has remained at this level. We are told of the staggering potential cost: up to $10 billion annually—greater than the entire health-care budget of many countries. And we are reminded of the distress and stigma caused by extreme SS among United States (US) children and adults. Why not proceed to balance cost and benefit and be done with the matter? What does it matter if SS, or even GHD, is really a disease or not?

I would like to present some ideas on this question in dialectic fashion, first stating an argument that declares the theoretical question irrelevant. This argument urges that we carry out the debate entirely on the policy level. I will then present an argument for the opposite position, of the need to consider the theoretical issues in their own right.

The Policy Argument

According to the argument that the policy level is the only relevant one (let me call this the "policy argument"), the belief that we must first decide whether SS and GHD are diseases stems from a misunderstanding of the nature of disease classifications. This mistaken view attributes to disease classifications an objective, scientific status that in actuality is only an illusion. The policy argument holds that deciding what a disease is and what it is not is a moral, political, or social question like any other. In support of this contention, observers have noted the wide variation among cultures in how diagnosis and classification are carried out. Lynn Payer, in her insightful book, *Medicine and Culture*,[1] notes:

> "Often, all one must do to acquire a disease is to enter a country where that disease is recognized — leaving the country will either cure the malady or turn it into something else. The American schizophrenic of a few years ago might well have found his disease called manic-depressive disease or even neurosis had he sought a second opinion in Britain; in France he likely would have been diagnosed as having a delusional psychosis. Blood pressure considered treatably high in the United States might have been considered normal in England; and the low blood pressure treated with eighty-five drugs as well as hydrotherapy and spa treatments in Germany would entitle its sufferer to lower life insurance rates in the United States."

Moreover, it is easy to find diagnostic categories that today are seen clearly to be instruments of social policy, whether or not they were recognized as such by clinicians of the past. The stock example is "drapetomania," a disease of slaves that impelled them to try to run away,[2] and there are many others.

One event in modern history seemed to clinch this view of disease classification: the decision in 1974 by the American Psychiatric Association to decide whether homosexuality should be deemed a disease by putting the matter to its membership for a vote. This step seemed to confirm the claim, pressed by the gay community, that the classification of homosexuality as a disease was an exercise of social control, a purely political phenomenon. The fact that it was settled by political means seemed appropriate as well as revealing.[3]

The precise sense in which disease classifications are to be considered social rather that scientific varies according to the theorist. At a minimum, diseases are said to be those variations in physiologic functions that deny people what they or society *value;* as values differ across society and societies, so do disease classifications. As with homosexuality, the classifications can be means of social control. The act of diagnosis can be a "performative" act, which means that it not only describes but also prescribes. Someone deemed sick by a doctor has an excuse not to go to work, for example, or, in the extreme case, may escape punishment for a crime.

Dr. John Lantos is quoted in the *New York Times Magazine* story on GH[4] as saying that shortness "has become a disease only because a manipulation has become available, and because doctors and insurance companies, in order to rationalize their actions, have had to perceive it as one." The policy argument would reply that some such story can be told for every disease classification. From this point of view, it makes little sense to complain that shortness is "wrongly" (unscientifically?) being called a disease. We must sit back and watch these social processes define diseases, as they usually do, even though it is open to us to join in and affect the process ourselves.

The Theoretical Argument

The view that disease classification is best understood as a purely social phenomenon, and that it is always "value-laden," dominated much of the debate over the concept of health until quite recently. However, the opposite point of view, one that insists diseases are objectively defined through medical science, has been made more plausible by the recent work of a few philosophers, most prominently Christopher Boorse.[5,6] Boorse and the others agree that many disease classifications have a value element, but they insist that these are embellishments (or, in some cases, distortions) of an underlying objective, scientific understanding of natural phenomena. What makes drapetomania so ludicrous is that it obviously is *not* a disease in any objective sense of the term; that it stands out among disease classifications is testimony to the lack of value elements in most of the others. Similarly, Boorse agrees that corresponding to the scientific concept of disease, there is a social role, the sick role, which involves value elements. Boorse wrote:

> A disease is an *illness* only if it is serious enough to be incapacitating, and therefore is:
>
> (i) Undesirable for its bearer;
> (ii) Entitled to special treatment; and
> (iii) A valid excuse for normally criticizable behavior.[5]

Boorse has since withdrawn even these concessions.[7]

Nevertheless, underlying these value or social elements is a scheme of classifications within the science of medicine that can be determined from an understanding of physiological function without regard to social attitudes. The function of the heart is to pump blood; this is a scientific fact, not a social convention. A heart that fails to pump blood well is a diseased heart; this too is fact, not a decision, performance, or value judgment. It may be that in our society an incapacitating disease excuses one from work; but the social fact here is the excuse, not the disease classification. When diseases are properly defined, they are scientific categories.

Thus, Boorse's view suggests that to pretend to decide whether SS is a disease purely on the basis of the social advantages and costs of doing so is quite wrongheaded. Either it is a disease, or it is not; let the chips fall where they may.

The Policy Importance of the Theoretical Considerations

If we accept Boorse's view of the objective nature of disease classifications, then in which direction are we pointed for policy purposes? It might seem at first that by moving diagnosis from the social to the scientific realm, Boorse has robbed it of any particular policy significance. This view would be congenial to that expressed by several authors in this debate, such as Allen and Fost,[8] ie, the etiology of a child's SS may be of secondary importance in determining the proper use of GH.

However, Boorse's analysis has proven to have considerable policy relevance, at least in the view of Norman Daniels, whose

book, *Just Health Care*,[9] has become the most influential theory of justice in health-care delivery. Daniels was drawn to Boorse's view on its own merits, but it turns out to have some favorable implications for those who, like Daniels, believe that society owes its citizens a basic minimum of health care. Perhaps surprisingly, Boorse's denial that disease is a value-laden concept is what makes his view congenial to these theories of justice. One might suppose that very broad, value-laden definitions of health and disease, such as the World Health Organization's definition equating health with overall well-being, would be favored by those who argue for a government role in ensuring access to care. However, the opposite is the case. If the concept of disease is purely social and value-laden, anything could be properly called a disease if social conventions so decided. But it is absurd to argue that societies owe their citizens everything. A more restricted view of what counts as a disease, such as that provided by Boorse, suggests a package of benefits we can credibly demand that governments deliver. Daniels's argument, which I will not repeat here, begins with Boorse's account, upon which he bases his view of social entitlements.

What conclusion could we draw from Boorse's writing, and that of Daniels, on the use of GH? This is a complicated question, and I will not be able to state a careful answer here. However, the answer most in the spirit of these analyses would seem to be that children who are short because their parents were short and who are otherwise healthy are not diseased: social values aside, there is no pathology. They are no more diseased than would be an Inca of similar stature who happened to be adopted by an American couple. And from this it would seem to follow, in the spirit of Daniels's theory, that no social entitlement exists for GH for short-statured children. However, there may be compelling social policy reasons apart from justice for providing GH to healthy short children.

This result may please some readers. Common sense seems to tell us that short people can be fully healthy, and that the social disadvantages of shortness are no more indicative of disease than were Jewish looks in Nazi Germany or the appearance of African ancestry in the Old South. And we may applaud the view that would deny any moral imperative to providing GH as a health-care entitlement, given the range of truly serious ailments that the same money could remedy. Thus, what may seem to be the commonsense views on both the policy and the theoretical levels are in a nice harmony.

Before ending, however, I would like to point to a possible source of trouble in this account. I do not believe that I am the only reader of Boorse's account of disease classifications who, while quite impressed and nearly convinced, has retained the suspicion that physiology is simply inadequate to define proper functioning, and that at some level the designation of a condition as a disease or pathology must make reference to social norms or conventions. GHD, in fact, seems to be a particularly revealing case. Allen and Fost[8] challenge their readers to make a meaningful distinction between 2 children destined to measure 5 feet, 3 inches: one whose shortness stems from GHD, the other whose shortness stems from inherited SS. With the first, it is true, we may find a particular organ that is not pumping out GH at expected rates; we may designate this a pathology, and the child as diseased. But why do we not designate the genetic inheritance of the second child as also pathologic? Those genes express themselves through some chemical pathway, perhaps not yet understood, which in a child expected to attain normal height might be regarded as pathological. Indeed, we might speak of a genetic disease if a child with tall parents suffered SS as a result of an independent mutation that produced precisely the genes that yield SS in children born to short parents.

Children of short parents, however, are regarded as "healthy" and their SS as "natural." One looks for an objective explanation for these disease classifications, but lacking that it seems plausible to attribute our classification behavior to social convention or tradition. We notice, and brand as pathological, that which attracts our attention as anomalous (and undesirable). Given our Danielsian instincts, which direct us to fulfill entitlements when we see real diseases, the person with anomalous distress may receive help while the person with distress we expect is called unlucky. Is this a fact about medical science or about human psychology and society? This line of questioning may, if successfully pursued, upset the comfortable harmony that seemed to hold between our best policy and theoretical views on SS and the allocation of GH. I suspect that they pose some difficulties for our theories of disease and of a just health care system as well.

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IS SHORT STATURE A DISEASE AND DOES THAT MATTER?

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Introduction

The question to be addressed is whether short stature (SS) is a disease and does its classification as such matter. In formulating an answer, we need to ask: Does it matter for what purpose SS is being classified as a disease? I will argue here that it is not necessary to conceptualize a condition as a disease in order to entitle its bearer to treatment, and also that there is no good reason to consider SS a disease. It is obvious that whether SS is a disease is not an issue to be determined by scientific discovery, but rather one to be decided on the basis of cogent reasons. Depending on which criteria are selected for what is to count as a disease, a case could conceivably (but not plausibly) be made for classifying SS as a disease. That classification would entail stretching the boundaries of the concept of disease beyond its usual limits. So it is important first to examine the reasons *why* it might be argued that SS should be considered a disease.

The Disease Label: Benefit or Burden?

According to one view, it matters a great deal whether a condition is classified as a disease:

> What hinges on the decision to refer to a process or state . . .by the word disease rather than be some other term? Obviously, a great deal. Medical attention, medical support, medical treatment, and medical research are devoted to the treatment, care, amelioration, and prevention of disease. . . Some groups have actively proselytized for the acceptance of certain conditions, such as alcoholism or gambling, as diseases. Other groups have worked to remove the label of disease from behavior such as homosexuality, masturbation, and schizophrenia.[1]

Although these observations about disease labels are true, they fail to indicate why those groups have sought to either embrace or shed the label of disease. A disease label can constitute a benefit or a burden. First, it can be a benefit if it results in the sorts of attention and treatment cited in the above quotation. Second, it can be a benefit if it serves to excuse an individual from behavior that would otherwise be blameworthy or culpable, as in the case of coprolalia exhibited by a person suffering from Gilles de la Tourette's syndrome. The desire to have alcoholism and gambling classified as diseases stems from these 2 reasons.

Yet diseases can also be stigmatizing. Perhaps the most extreme case is leprosy, and somewhat less so, epilepsy. A current example is AIDS. Until quite recently, cancer was a stigmatizing disease and people were ashamed to admit to a diagnosis of cancer. And in some social and cultural groups even today, psychiatric diseases remain highly stigmatizing.

But SS differs from all of these in one key respect. It is the physical condition itself that is the stigmatizing factor, regardless of whether it bears a disease label. A decision that SS deserves to be considered a disease would not contribute an additional stigma, nor could it serve to act as an "excusing" condition in any way similar to the other diseases or disorders just mentioned. Socially undesirable behavior is different from aesthetically undesirable body build because people are blamed for the former but not for the latter.

But is that always true? Consider obesity. In years past (perhaps today as well) it was not uncommon to hear people "excuse" their obesity by saying it stemmed from a thyroid condition. There is surely an etiologic difference between obesity that stems from an underactive thyroid and obesity that results from overeating. Consequently, the former may be a more "excusable" body build than the latter. Obesity itself is not a disease, although it is correlated with all sorts of diseases. Yet children as well as adults may be just as handicapped by being obese as they are by being abnormally short. I will return to this comparison later in addressing the question of whether it matters if SS is a disease.

Why Consider Short Stature a Disease?

If a condition has to be conceptualized as a disease in order to entitle its bearer to medical treatment, then that would be a reason to argue that SS is a disease. The presupposition is that a "yes" answer to the question whether SS is a disease entitles an individual to medical treatment that could ameliorate the condition and that a "no" answer would carry no such entitlement. I will try to show why this presupposition is wrong.

Specific reasons that might be used to support the claim that SS is a disease fall into different categories. For ease of reference, I use the following arbitrary, shorthand labels for these categories: (1) medical intervention, (2) insurance and other entitlements, (3) social policy, and (4) psychosocial consequences.

1. Medical intervention. Growth hormone (GH) therapy is undeniably a medical intervention. Hormones can have side effects, possible toxicity, and other complications. Their administration requires medical expertise and for that reason should remain in the hands of medical professionals. Because medical professionals are qualified and authorized to treat diseases, SS should therefore be considered a disease.

This argument embodies several different presuppositions. First, it assumes that if SS is not a disease, then physicians might not be permitted to offer GH to patients. Conversely, if SS is a disease, then control over decision making about the use of GH should be left in the hands of medical professionals.

The first reply to this argument is that physicians can and should be involved in prescribing and monitoring the use of GH whether or not SS is a disease. GH is a pharmaceutical product that might pose risks to users and may be contraindicated for use in some patients. Therefore, it is reasonable to vest control over its use in the hands of physicians, whose expertise is required for excluding medically unsuitable candidates and whose ethical obligation is to seek the best outcome for each individual patient.

A second reply is that a large number of different conditions treated by physicians are not diseases and there is no call for classifying them as diseases simply because physicians are or must be involved in treatment programs. One example is obesity. Overweight people go to doctors for weight loss programs, for medications that can aid them in dieting, and for surgical procedures such as liposuction. Although obesity places people at elevated risk for a wide variety of diseases, being fat is not a disease. It does, however, carry many of the same social consequences as being short. For another example, plastic and reconstructive surgeons perform many procedures, ranging from cosmetic enhancements to correction of disfiguring facial anomalies. Although some of those conditions may be associated with underlying diseases, they are not themselves diseases. Nevertheless, surgery must be performed by members of the medical profession.

2. Insurance and other entitlements. Since 2 other presentations at this conference address the question of insurance reimbursement and whether GH should be an entitlement in the allocation of health-care resources, I can safely dodge those issues here. However, it is worth emphasizing that entitlements to insurance or health-care resources often have little or nothing to do with how a particular condition is classified and whether the classification constitutes a disease.

Not everything that is a disease gives rise to a particular entitlement, and many things that are not diseases do give rise to entitlements. For example, there is no controversy over whether the numerous malfunctions, impairments, and deteriorations that comprise heart disease are really *diseases*. Yet there is no entitlement to a heart transplant or (in the days when Jarvik and De Vries were very busy) to an artificial heart.

Or, to take some examples on the opposite side, pregnancy is not a disease, despite the fact that it has been "medicalized" and medical complications can arise. Insurance pays for prenatal care, and the call for better allocation of prenatal services to poor women and teenagers does not rely on an assumption that pregnancy is a disease. Additional examples abound in the sphere of mental health. Clinical psychologists use the diagnostic category "adjustment reaction to stress" to obtain insurance reimbursement for clients, but there is typically nothing about those individuals' feelings or behavior that would warrant a diagnosis of psychiatric disease. Finally, ignorance is not a disease yet an entitlement exists to education in societies that provide free, public education to children. So it is clear that there may be entitlements to some social goods whether or not the human need for those goods stems from a condition that can properly be called a disease.

3. Social policy. To classify a condition as a disease would appear to place its bearers in a position to benefit from certain social policies, for example, antidiscrimination clauses that prohibit barring individuals from school or employment based on their disease. Alternatively, having a disease might qualify an individual for certain positive benefits, such as sick leave, home care, or other special services.

There are several different replies to this argument. First, an individual need not be placed in a disease category in order to qualify for protection against discrimination, as the civil rights and women's movements clearly demonstrate. Second, there are useful conceptual categories other than disease on which social policies can rest, for example, impairment, disability, and handicap. If SS does, in fact, constitute a handicap or disability to individuals, it is not necessary to classify it as a disease in order for benefits to accrue to such individuals. Third, social policy can authorize paid leave or other employee benefits for circumstances that have nothing to do with disease, disability, or handicap. An example is maternity leave and, in its expanded version, paternity leave following the birth of a child. Whether a social policy serves to prevent discrimination or provide benefits, a condition need not be shoehorned into the category of disease in order to qualify.

4. Psychosocial consequences. Children and adults who are abnormally short can suffer unhappy psychologic consequences as a result of their condition. If they are socially unpopular, fail to attain positions of leadership, or otherwise perceive barriers to their advancement that might be attributable to SS, they might become chronically depressed or anxious. Similarly, these barriers close off opportunities that would be open to individuals who are of average or taller than average height. This argument would contend that suffering such social and psychologic consequences should qualify abnormally short individuals as having a disease.

Many things cause people to become depressed or chronically unhappy that clearly are not diseases: unrequited love, financial loss, the death of a loved one, and failure to make the football team, to mention only a few. The fact that a condition or circumstance gives rise to psychologic consequences in the individual who experiences it has nothing whatever to do with whether the condition is a disease.

As for the social consequences of being abnormally short, appropriate concepts are already in use and are more suited to SS than is the concept of disease. Ones already mentioned are impairment, disability, and handicap. In addition, the concept of malady has been proposed[2] as a general term, broader than that of disease, dysfunction, handicap, or disability, and encompassing all of these. It is defined as follows:

> "A person has a malady if and only if he or she has a condition, other than a rational belief or desire, such that he or she is suffering or at increased risk of suffering, an evil (death, pain, disability, loss of freedom or opportunity, or loss of pleasure) in the absence of a distinct sustaining cause."[2]

Does It Matter?

There are numerous examples of statistical deviations from normalcy that are not considered diseases, such as intelligence. In the case of Down syndrome and other genetic conditions, lower than average intelligence has a biologic substrate. If it were possible to intervene in utero to correct this chromosomal anomaly or others like it, it would be irrelevant whether the condition were termed a disease. Whether lower than average intelligence ought to be "fixed" (were it possible to do so) does not depend on whether it is termed a disease, or even whether its etiology can be considered a disease. Even in cases where no genetic or other biologic underpinning can be ascertained, now or in the future, if low intelligence could be improved by medical intervention, what argument could be given to show that it would be ethically wrong to do so? Only if the potential medical risks of the intervention outweighed the expected benefits of achieving normal intelligence could an ethical argument be mounted.

Suppose there were a successful medical treatment for obesity. Would we have to ask, first, whether obesity is a disease before we are prepared to offer it to parents for their children? If not, it is probably because obesity places an individual at risk for so many serious or life-threatening conditions (even if they mostly occur later in life). Like obesity, SS often places people in our culture at a distinct social disadvantage. But unlike obesity, SS is not correlated with other potentially harmful diseases. Obesity fits more comfortably within a medical model than does SS, but that fact alone does not show that it is ethically inappropriate for physicians to offer GH to parents of abnormally short children.

I can think of only one compelling reason why it might matter whether SS is considered a disease. That reason relates to the professional duty of physicians to mention treatment options and to offer therapy from which patients could benefit. If SS were to be considered a disease, a standard of care would evolve obligating physicians to offer GH to patients (or the parents of patients) who have the "disease."

However, what physicians mention among available options for patients should not be a function of whether the patient's condition is classified as a disease. The risk-benefit ratio is one of the factors that should determine what physicians are obligated to offer their patients. Assessing that ratio, along with the other factors, may not be an easy task. But whether the patient's condition falls into the "disease" category is irrelevant to the physician's obligation.

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DISCUSSION III: A & B

A. Theoretical and Policy Debates Over the Status of Short Stature as a Disease - Daniel Wikler, PhD

B. Is Short Stature a Disease and Does That Matter? - Ruth Macklin, PhD

Moderated by Norman Fost, MD

WIKLER: What is fairness in society? Most of us carry our ideas about this around in our heads, but do not listen very well. That leads to some very strange and arbitrary judgments. For example, we agree that it is perfectly fine for workers to compete for jobs even though there is unemployment. One is smarter than another, but the smarter one does not always get the job. However, if a person is mentally retarded, he or she may be *guaranteed* a job based upon the handicapped status, with certain jobs being reserved for this group of individuals. Our social perspectives set forth that it is unfair for an individual to be denied or to receive certain privileges and status based upon intellect. An underlying societal conflict is that we want to live within a competitive system, based upon some guarantees or provisions for certain intrinsic benefits, yet at the same time, we have less appreciation for some of the effects of this system. So we selectively participate in and perpetuate an arbitrary system in which some physical attributes are perceived as handicapping—and thus warrant protective measures—while other conditions are perceived as less severe and are not supported by the system in the same manner. We label one condition a handicap, which

WIKLER: translates into a protected status and societal management attempts to ameliorate some of the effects of this competitive system.

Both this question and Dr. Macklin's response imply that growth hormone-deficient and GH-responsive children should be treated in the same manner. We may not yet be able to decide what constitutes a handicap, but it would be the same for both children assuming there are no medical consequences due to growth hormone deficiency other than short stature.

FOST: Thus, a person who is growth hormone deficient and destined to achieve a final stature of four feet six inches would be no more or less entitled to treatment than a nongrowth hormone-deficient individual with an equivalent projected final height. Either *both* individuals are entitled to treatment or neither is. Do you agree with this?

MACKLIN: Yes. In fact, I apologize because I did not draw that conclusion explicitly in my paper.

CALLAHAN: We have conventionally defined many things, as physicians do, by way of offering treatment. Society permits and supports this approach. However, if we look ahead to the entitlement debate, our crisis at this point is deciding when and where to draw a line on some of these very casual conventions we have allowed to develop. Can we find better standards than societal conventions for assessing entitlement to treatments physicians may provide? Utilizing a strict risk/benefit standard, we could, for example, have physicians presenting a valid position for addressing and managing the threat of nuclear war with the equivalent decision-making power as the State Department, and so forth. Can physicians provide more substantive criteria? And if our decisions are to be based upon a risk/benefit ratio, there should be a relationship to actual physiological status, as opposed to cultural or societal conventions.

MACKLIN: One reason that physicians should be involved in this decision-making process is that an expertise is required for both the clinical examination of patients and in administration of the treatment. Here I am specifically addressing the *clinical* aspects of services that physicians offer to patients. A distinction needs to be made between whether physicians are *obligated* to offer these services or whether physicians may be *permitted* to offer these services. In resolving the entitlement issue, I think we have to grapple with the question of *obligation*.

CALLAHAN: One of my reasons for supporting a fairly rigid medical standard (namely, some kind of physiological deficiency), is that this affords one the basis to make some consistent policy decisions.

MACKLIN: My argument is that a condition does not have to be defined as a disease in order for a physician's expertise to be relevant to patient management.

CALLAHAN: Yet consider that several of the cases you mentioned have some ultimate biological consequences.

FOST: Pregnancy is covered because of the importance of preventing medical complications, such as hypertension, diabetes or prematurity, when, in fact, one does not need a physician to manage a *normal* pregnancy.

MACKLIN: But you do need physicians, I presume, if you are going to be administering hormones that have physiologic effects that need to be monitored. We do not want the disability expert to be prescribing and treating with growth hormone.

DANIELS: Many technologies that slowly become the province of physicians (eg, cosmetic surgery) involve very sophisticated techniques that only physicians are qualified to perform; yet there is a widespread perception that despite the advantages that meeting some cultural standard of attractiveness might confer on individuals, it is *not* a social responsibility to make sure that this sort of service is an *entitlement*. Most healthcare systems are inclined to deny coverage for cosmetic surgery, whereas *reconstructive* plastic surgery is frequently an entitlement. By what criteria is this distinction made? *This* is an important question to answer. The issue is not solely what falls in the purview of the expertise of physicians. I would suggest that the key moral and policy question is this: which inequalities; that is, which individual differences, create obligations (or entitlements) on others to correct for the inequality? If we get away from what physicians actually *do* and what insurance companies have historically covered, and focus on resolving the underlying question, what gives use to a social obligation to medical services, then maybe we can arrive at some reconstruction of what is appropriate for inclusion as an entitlement in our healthcare system.

WIKLER: I think both Drs. Daniels and Callahan are hoping for an objective, physiologic definition of disease which will elucidate what this healthcare system owes each of us. Suppose that I (who is very tall) had a son who was born very, very short, due to a new genetic mutation. Does my child have a new genetic disease or a physiological defect? Given that short stature is not expected in my family, my guess is that it would be considered a failure of physiological function and therefore, a disease entity. Yet, if I adopt an Incan child, my short son might grow to be taller than the Incan child, yet the Incan child would, in fact, be considered perfectly normal.

CALLAHAN: If you consider it a disability to be short, then demonstrate the cause (eg, the mutant gene). If you determine that the etiology is due to a mutant gene, then insurance companies will provide coverage for the treatment.

WIKLER: Suppose the mutant gene turns out to be identical with the Inca's natural genes. Now what? (laughter)

HINTZ: Look for an Incan father. (laughter)

WIKLER: The Incas are fine. They are all happy and healthy. They are short and they are healthy. My kid has got a mutant gene and he is sick. They have the same gene, however. My claim is that ultimately this is a cultural determination or stipulation.

MENZEL: I want to pursue whether we should be treating the *social* prejudice or the *physiological* state. I agree entirely with your analysis of intelligence as an example. There is a good reason why intelligence is considered in a job situation and why society may want to pursue that track and support people with low intelligence. But what can you say for making judgments on the basis of stature once you are off the basketball court? Very little. Therefore, it is debatable whether medicine should be the proper avenue for addressing the problem.

LUSTIG: What we label a disease evolves over time. Even a decade ago, gambling and alcoholism were not considered diseases, but now they are. Two criteria, define diseases. Firstly, there must be a biological cause. Today, we are considering genes for alcoholism. With gambling, we are examining the change in CNS dopamine receptors. Homosexuality is not far behind with a new focus on the structure of the hypothalamus (reported in *Science* recently). Secondly, whether or not something gets labeled a disease by society is whether there is stigmatization associated with it. Short stature has a biological cause and stigma associated with it; so doesn't that qualify it as a disease?

WIKLER: Actually, I disagree with most of your examples. Suppose we discover that there is a part of the brain that *is* different in homosexuals—or a physical correlate of the behavioral difference. This does not qualify it as a disease rather than a variation.

LUSTIG: No, absolutely not. But there are a lot of people who are actually starting to think about it in that light. In fact, the homosexual community may be happy to be relieved of the burden of origin. We can also ponder that if society started calling homosexuality a disease, would we then start looking for therapies?

DANIELS: It is really not enough to simply say that there is a physical correlate, competency to treat, or a stigma for a condition to be labeled a disease. Much of cosmetic surgery is done to correct conditions that have physical correlates of impairment and some degree of social stigma, but we do not, by any means, consider them diseases.

BAILY: I heard this morning that there is a definite difference in the benefits of GH treatment for GH-deficient versus idiopathic short children. Now to me, as an economist, that is a very solid reason for distinguishing between these two groups and for determining entitlement to treatment. But how do you handle the issue of short stature as a "handicap?" Prescribing growth hormone for "handicapping" short stature is extremely expensive. If my child had a birthmark, it would not be reasonable to attempt to have everyone "forget" or ignore birthmarks. I would seek laser treatment for the child. The therapy would be relatively inexpensive to achieve the effect. I do not care whether it is a disease or not. The question is, what are the benefits relative to the cost of using an entitlement program?

HINTZ: You (Dr. Baily) make the assumption that the most GH-responsive children should be distinguished by GH secretion testing. I do not think that's true. Groups of children we call classically growth hormone deficient may or may not respond better in the first year. There is a huge overlap, and we cannot accurately, prospectively pick out those children that are going to respond.

FRASIER: However, there are groups of children, that should be treated, such as children with craniopharyngioma—children who do not grow and have no growth hormone response.

GERTNER: The child (patient) is usually not the individual who is being asked what they want and how they see the future. This comes from the parents, which makes it difficult to know how much is really decided by the patient and how much is, as it were, forced on them through social factors and social conformity.

LANTOS: I have just been writing down some of the diseases that people have been bringing up as analogies to short stature — obesity, homosexuality, minor facial abnormalities, and gambling. And it does not seem like such a strong argument to say that because doctors have dealt with these or called them diseases, that short stature should be managed in the same manner. There is another category of diseases (like heart disease, cancer, diabetes) that are unambiguous and so do not require consideration for this policy. It seems like what we are doing is acknowledging that short stature is more like gambling than cancer.

ALLEN: We erroneously use the term "short stature" as a diagnosis that has fairly uniform meaning. I suggest that

ALLEN: entitlement to growth hormone therapy should not be dependent on diagnosis, but rather upon disability. Entitlement to a variety of medical treatments should be based on an individual's inability to take advantage of opportunities within a normal range regardless of the degree of, eg, facial disfigurement or other handicapping feature. What is the degree of disability that results from extreme short stature, and under what circumstances can we consider someone "entitled" to help for this disability, regardless of the etiology? When we talk about the basic healthcare needs that our society is responsible for providing, at some point we have to make this type of decision, (eg, determine where "handicap" begins). Is this a concept that can be applied to short stature?

WIKLER: Americans talk about equal opportunity. How seriously do we mean that? Do we *really* want to equalize opportunity for everyone? Well, that is preposterous because we would have to intervene in every aspect of our private lives! I am the tallest person here. So if that is an advantage, should I be handicapped in some other way so that the shortest person here would begin at an equal level as I? If we really mean equal opportunity, the intervention required would be so enormous that it would require an interventionist state like we have never seen before. A fallback position is this — there are certain features that have natural advantages. Thus, we select characteristics and differences between people and designate certain ones as unfair. Other characteristics will not be considered. Once we have created ways to level some of these inequities, we will have achieved equal opportunity or close to it.

MacGILLIVRAY: Some of the confusion about short stature is related to the terms we use. Dr. Wikler used the phrase normally short, nongrowth hormone deficient children. Children who are growing along the 3rd, 10th, and 25th centiles have a normal growth rate and can be appropriately classified as "normally short." However, another name needs to be applied to pathologically short children with subnormal growth rates. Currently they are described as having idiopathic short stature and this causes confusion because the term short stature is being used for children with innocent short stature as well as for children with pathologic growth. I prefer to refer to the latter group as idiopathic growth failure and consider GH therapy appropriate for some of them because their abnormal growth velocities will prevent them from achieving their genetic endowment. If we continue to use the term normally short child for children with pathologic growth, we are conveying to the public, to the insurance companies, to philosophers and to economists that these children are normally short when they are not.

WEISBARD: Our definitions of disease seem to be driven by the availability of a potentially efficacious medical intervention and the existence of a group of physicians who can and would like to use that intervention, with the hope of benefitting some "patients." I recently attended a conference considering whether infertility is a disease, and what sorts of medical and societal responses are appropriate. There was widespread consensus that surgical "plumbing" repairs for both men and women should be an entitlement. There was disagreement as to whether IVF and more exotic modes of assisted conception should also be covered. Interestingly, there was near consensus regarding another potential response to biological infertility. Most participants felt that adoption-related services should *not* be covered, even though adoption might represent a less expensive, more certain, and socially quite appropriate, way of responding to the desire for a child when a couple cannot conceive naturally. I disagreed with that conclusion, and would argue here that availability of medical treatment is almost morally irrelevant to our social judgment about what priority should be given to the treatment of short stature, compared to other social needs. I would urge further consideration of Dr. Menzel's suggestion of a trust fund to support a variety of approaches, not necessarily all pharmacological, to the range of psychosocial problems associated with short stature. Of course, this implies rethinking the way we define and utilize what we now call "health" insurance.

DIEKEMA: We should not minimize the importance of classifying problems as diseases, since such a categorization tends to lead to entitlement for insurance benefits. Insurance companies often require a medical diagnosis before they will pay for services. Short stature does not fit nicely into the category of disease, and so we may need to look for other reasons that support entitlement to growth hormone therapy.

MACKLIN: There are some entities that do not fall into the same category because we take them for granted—at least in this society (and always have), in contrast to medical care, that are an entitlement. One of these entities is education. Education is a social good to which everyone is entitled, unlike healthcare, which is still not viewed as a right or social good. It is not necessary to call ignorance a disease in order for there to be a social entitlement to education. This represents a peculiar historical aspect of the United States of America, where it has never been questioned whether education is an entitlement (although this is not the case in many other cultures). Oddly enough, however, we remain one of the few societies who do not consider medical care an entitlement. Should there be free public education for everyone? If you had fewer people educated, you might have more people performing unskilled labor and perhaps a better distribution of jobs in the society that would run more efficiently.

CHARO: I agree with the comment that a lot of this has to do with the simple creation of a new tool. Furthermore, I think this is really a debate not about disease or entitlement, but about the locus of control for this new tool and the implications of its use to circumvent social prejudice. We have all agreed that extreme shortness can be a disability

CHARO: due more to societal prejudice than to functional impairment. Because physicians understand the techniques, they can evaluate the risks and the benefits on a physical level (or the likely effectiveness of growth hormone therapy for this particular person), and, therefore, they may be the most appropriate locus of control. But that may not be the case. The victims of prejudice are in the best position to balance for themselves what risks they are willing to take on in order to circumvent this prejudice. True, victims often make stupid decisions on their own behalf. But physicians do not view themselves simply as the people with tools to be put to use for other people. Most physicians think of themselves as healers or caregivers to the whole person and do not view themselves in this more humble, restricted fashion, whether it is to cure a plumbing problem or to circumvent or overcome a social disability with a medical tool.

FRASIER: In looking at alternative approaches to the problem of short stature, there are other therapeutic agents that may be effective, safe, and less costly (eg, anabolic steroids). These have been used for years in the management of short children with a variety of conditions.

GERTNER: The point I would like to address is related to the question: Does it matter whether short stature is a disease? As pointed out beautifully before, disease is relativistic in time and space. If, in this time and in this space, people think that short stature does matter, regardless of its being a disease or not, is that enough to make it matter?

MACKLIN: Could we just simply go ahead and call it a disease? There are a lot of things that people think matter. Being a philosopher, I can talk in "oughts." The question is, ought it to matter as much to people as it does? And here we have to look at the social barriers, the psychological consequences, and how people have lost opportunities caused by being abnormally short, regardless of whether they have sufficient secretion of growth hormone. I saw a TV program about cosmetic surgery in southern Califomia where extremely attractive teenagers were going in to have chin clefts and tucks and the like. To these "Valley Girls" and their moms, it matters, but is that to say it ought to matter? No. If we had more evidence regarding social barriers, the stigma leading to actual discrimination, handicap, and the loss of opportunity, then I think that could provide objective evidence that it does matter.

FRASIER: I must object to the stereotyping of southern Califomia teenagers. (laughter)

TESCH: As a person with Tumer syndrome who has to deal with extreme short stature and complete infertility, I would like to point out that it is not just the social perception and psychological discrimination that create the desires and hopes for GH treatment. It is also the fact that there are physical opportunities that are completely lost, closing off certain opportunities to these individuals from normal functioning in society. Whether it is driving a car, buying clothes, or finding appropriate marital opportunities, you know that you have these physical handicaps, and lack some capabilities that almost every other person in the world has.

MACKLIN: Well, this goes back to the discussion that we had a moment ago regarding whether or not there ought to be other kinds of entitlements that society should provide. Think of all of the legislation and the entitlements that people with various disabilities have, whether it is the hearing impaired, the visually impaired, or others. There are ways in which social decisions have been made to modify the environment for people who have these various handicaps to enable them to do things more easily. We can probably think of several examples. Perhaps the clothing manufacturers might be one of the first places to look. That is, women of extreme short stature should not have to buy their clothes in the little girls' department. Society might make certain provisions for people with extreme short stature in the same way that we have made adaptations for the hearing impaired or vision impaired.

FOST: Thank you very much.

GROWTH HORMONE THERAPY FOR SHORT STATURE: CAN WE SUPPORT THE TREATMENT/ ENHANCEMENT DISTINCTION?

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Medical Need and the Scope of Obligations to Treat

Many medical technologies, new and old, can alter people in ways they desire to be changed. When do we have a social obligation to ensure that such preferences are met? Do rights to health care include entitlements to have those preferences met, resources permitting? What should insurance cover?

The most inclusive answer to these questions is that we have such obligations whenever someone desires to eliminate an unwanted physical or mental condition. This would allow subjective preferences to place enormous demands on resources, holding us hostage to the extravagant tastes of others.[1,2] Since we do not believe it is medicine's task to make everyone equally happy, we reject this view and its implication that we should have to pay for liposuction or face lifts. Instead, we think obligations arise only when medical treatments address more important problems.

A less inclusive answer is that we have such obligations whenever people desire to eliminate conditions that put them at some disadvantage. The notion of disadvantage is meant to be objective, including some forms of suffering as well as the competitive disadvantages that result from lack of capabilities, such as marketable talents or skills. When disadvantages are not the result of prior choices or personal fault, the view has some initial grip on us. Our egalitarian inclinations may lead us to think we owe something toward eliminating them.[3,4] But this still assigns medicine too great a role as a social equalizer. It is not medicine's task to make everyone an equal competitor, eliminating wherever possible all inequalities in the distribution of talents and skills or other capabilities.[5]

A more modest answer that tends to match a wide range of our practices, including our insurance practices, is that we have obligations to provide services whenever someone desires that a medical *need* be met. Generally, this is taken to mean that the service involves *treatment of a disease or disability*, when disease and disability are seen as departures from species-typical normal functional organization or functioning.[6,7] Characterizing medical need in this way implies a contrast between uses of medical services that *treat* disease (or disability) conditions and uses that merely *enhance* human performance or appearance. Enhancement does not meet a medical need even when the service may correct a competitive disadvantage that does not result from prior choices. Accordingly, medicine has the role of making people *normal* competitors, not *equal* competitors.

Challenges to the Treatment/ Enhancement Distinction

Despite its wide appeal, the distinction between treatment and enhancement seems arbitrary in light of hard cases like these:

> Johnny is a short 11-year-old boy with documented growth hormone deficiency resulting from a brain tumor. His parents are of average height. His predicted adult height without GH treatment is approximately 160 cm (5 feet 3 inches).
>
> Billy is a short 11-year-old boy with normal GH secretion according to current testing methods. However, his parents are extremely short, and he has a predicted adult height of 160 cm (5 feet 3 inches).[8]

These cases make the distinction seem arbitrary for several reasons. First, Johnny and Billy will suffer disadvantage equally if they are not treated. There is no reason to think the difference in the underlying causes of their shortness will lead people to treat them in ways that make one happier or more advantaged than the other. Second, although Johnny is short because of dysfunction whereas Billy is short because of his (normal) genotype, both are short through no choice or fault of their own. The shortness is in both cases the result of a biologic, "natural lottery."[9] Thus, both seem to be undeserved disadvantages. Third, Billy's preference for greater height, just like Johnny's, is a preference that most people hold; it is not peculiar, idiosyncratic, or extravagant. Indeed, it is a response to a social prejudice. The prejudice is what we should condemn, not the fact that they both form an "expensive taste" in reaction to it.

Other hard cases not involving GH treatment also challenge the treatment/enhancement distinction. Consider gynecomastia:

> Ben has significantly enlarged breasts. The enlargement is the result of a prostate tumor. Bob has significantly enlarged breasts. The enlargement is a side effect of hormone treatment he is receiving for another medical condition. Bert has significantly enlarged breasts. The enlargement is the result of his taking anabolic steroids to promote muscle development. Bruce has significantly enlarged breasts. The enlargement is not the result of any diagnosable disease condition.[10]

Medical insurance usually covers Ben and Bob for the surgery involved in treating their conditions. Bert may have coverage as well, though his "responsibility" for assuming the risks of a prior enhancement therapy raises questions not faced by Ben and Bob. Bruce, however, will generally have to pay for his own breast reduction. Still, all of them will suffer equally if not treated, and their preference for breast reduction is not idiosyncratic but socially conditioned. It is also clear that Bruce, like Ben and Bob, is not in any way responsible for his condition.

These hard cases raise the following questions: Does the concept of disease underlying the treatment/enhancement distinction force us to treat relevantly similar cases in dissimilar ways? Are we violating the old Aristotelian requirement that justice requires treating like cases similarly? Is dissimilar treatment unfair or unjust? This moral question must be addressed separately from another question: even if it is not obligatory to provide GH therapy that merely counts as enhancement, is it permissible to do so? Some argue that GH for short but otherwise normal children violates ethical norms because of the uncertainties concerning risks and benefits.[11] In a sense, this is a prior question: if it is not permissible to enhance the height of short normal children with GH, then it can hardly be obligatory to do so. Still, I shall not address this question here. I focus on the philosophic issues involved in the treatment/enhancement distinction because they are of general importance and are independent of our current uncertainty about the risks and benefits of GH therapy.

The Treatment/Enhancement Distinction and Equality of Opportunity

Despite the challenge of hard cases, the treatment/enhancement distinction should play a role in deciding when we are obligated to provide medical services. To show that this distinction is not arbitrary from the point of view of justice, despite the hard cases, I shall argue that it fits better than alternatives with what I shall call the *standard model* for thinking about equality of opportunity. Of course, the standard model may be indefensible. That is a much broader question, one I cannot adequately address here. Still, I can show the standard model helps specify a reasonable limit on the central task of health care.

Disease and disability restrict the range of opportunities open to an individual. Health-care services maintain, restore, and compensate for losses of function that result from disease and disability. They thus restore people to the range of capabilities they *would have had* without disease or disability, given their allotment of talents and skills. Our *standard model* for thinking about equality of opportunity thus depends on taking as a given the fact that talents and skills and other capabilities are not distributed equally among people. Some people are better at some things than others. Accordingly, we assure people *fair* equality of opportunity if we judge them by their capabilities while ignoring "morally irrelevant" traits like sex or race when we place people in schools, jobs, and offices. Often, however, we must correct for cases in which capabilities have been misdeveloped through racist, sexist, or other discriminatory practices. Similarly, by preventing or treating disease and disability, we can correct for impairment of the capabilities people would otherwise have. The standard model does not call for our eliminating all differences in capabilities through medical enhancement.

This limitation of the standard model can appear arbitrary. As I noted earlier, our capabilities are themselves the result of a natural and social lottery, and we do not "deserve" them. We just are fortunate or unfortunate in having them. We can mitigate this underlying arbitrariness *somewhat* as follows. Those who are better endowed with marketable capabilities are likely to enjoy more goods such as income, wealth, and power. If we constrain inequalities in these goods so that those who are worse off do as well as possible, considering all alternatives, then social cooperation will work to the benefit of all.[9] Still, this constraint does not eliminate all inequalities in the capabilities people have and thus in the opportunities individuals enjoy, especially since we enjoined to judge people in light of their capabilities. If our egalitarian concerns require that we strive to give people equal capabilities, wherever technologically feasible, then we should not settle for mitigating the effects of this reliance on equality of opportunity as standardly understood.[12] Rejecting the standard model pushes us toward leveling all differences in capabilities; from that perspective, the distinction between treatment and enhancement has no point.

From the perspective of the standard model of fair equality of opportunity, however, it is reasonable to limit the task of medical services to restoring people to normal functioning and thus the range of opportunities they would have had absent disease or disability. In the standard model, the treatment/enhancement distinction retains its point. For purposes of justice, it is enough that the line between disease or disability and its absence is *uncontroversial* and *ascertainable through publicly acceptable methods,* such as those of the biomedical sciences, for the general run of cases. Being able to draw a line in this way allows us to refer counterfactually in a relatively clear and objective way to the range of opportunities a person *would have had* in the absence of disease and disability; it facilitates public agreement. My claim that we have obligations to provide health-care services that meet people's medical needs, within resource limitations, thus derives from accepting the standard model for thinking about fair equality of opportunity. Abandoning the treatment/enhancement distinction would push us toward a much more radical form of egalitarianism. I can here neither defend nor criticize such a view, except to point out that dropping the distinction does not

just open the door to GH therapy for short normal children, eliminating one anomaly. It begins a cascade of changes in the scope of medicine that would forever change its face and might threaten the social consensus that gives medicine the strong moral grip it has on us and our resources.

It might be thought that we do not need to adopt such an extreme position if we abandon the notion of disease or disability. If extreme shortness could be considered a "handicapping" condition, then we might still be able to appeal to the standard model of equality of opportunity.[8] GH therapy would simply move people into the range of capabilities they would have had were they not "handicapped." This "compromise" approach does not seek full equality in capabilities, only the end of handicapping disadvantages.

There are serious objections to dropping the reference to disease in drawing this version of the treatment/enhancement distinction. First, we need a clear notion of "handicap." Specifying the shortest 1% of individuals as "handicapped" will itself seem arbitrary after the first cycle of therapies creates a new group of shortest people. Not treating the newest group would then seem arbitrary in light of a new set of hard cases. Second, it will now be medicine's task to eliminate all comparable handicapping conditions. In our racist society, this means black or brown or red skin. Should we eliminate the melanin or oppose discrimination? Although the compromise approach does not seek equality of capabilities, it vastly expands the function of medicine and, by medicalizing social problems, risks losing whatever consensus exits on the moral importance of meeting health-care needs.

Two further points should be made in defense of the treatment/enhancement distinction. First, the problem raised for it by our hard cases is similar to the kind of problem all rules face when their justification derives from the fact that general conformity to them is on the whole either better or fairer. We can almost always describe hard cases in which the very reasons that lead us to adopt a rule to cover the general case also lead us to think the rule is nonoptimal or unfair when applied to them. Though troubling, hard cases do not always count as counterexamples that force us to reject the rule. Sometimes we must swallow the discrepancy between the particular case and the general run of things if we want a generally better or fairer distributive scheme.

Second, not all of our social obligations to provide treatment for people derive from the central considerations of justice to which I appealed in my account. For example, we have compelling reasons for providing public funding for nontherapeutic abortions, which do not count as meeting a medical need (prevention aside). The social obligations that derive from these reasons may be as compelling as the considerations of justice I claim are central. It is important, however, when considering public policy to keep our lines of argument distinct. We may well develop reasons for thinking certain enhancements are as morally important to provide as some treatments. Still, these reasons will differ from the concerns about justice that provide the central justification for rights to health care.

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Session IV:

SOCIOECONOMIC ISSUES RELEVANT TO THE TREATMENT OF SHORT STATURE

Editor's comments: While market forces may eventually reduce costs, the present reality is that growth hormone (GH) therapy is extraordinarily expensive. Questions of entitlement, therefore, depend not only on considerations of efficacy and risk-benefit analysis but also justification of the cost-benefit analysis. What would it cost to expand the population eligible for GH therapy? Should private insurance financing be expected or public financing supported? What health-care resources should be allocated to the treatment of short stature? In this session, these questions are examined from insurance, economic, and philosophic perspectives.

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GROWTH HORMONE THERAPY FOR CHILDREN WHO ARE NOT GROWTH HORMONE DEFICIENT: SHOULD INSURANCE COMPANIES PAY FOR THE TREATMENT?

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Introduction

Deciding what services ought to be reimbursed by third-party payers in this country is a complicated process. It asks us to consider our social priorities, while calling into play information from medical science and economics. Criteria must be identified to determine to which services individuals should have access; then it must be decided whether a given service satisfies those criteria. Determining whether children of short stature (SS) who are not growth hormone deficient (GHD) should have human growth hormone (GH) therapy reimbursed by insurance companies is a prototypical decision in this process.

Once GH could be produced synthetically and was no longer in short supply, a new group of individuals, comprised predominantly of parents of non-GHD short children, started to inquire about gaining access to the drug. Although certain reasons offered for their requests concerned potential functional limitations (eg, inability to reach the pedals of a car), more frequently psychosocial justifications were provided, including that the child would have better opportunities, increased social acceptance, and, ultimately, greater self-esteem, if he or she could receive injections of GH.

This paper will discuss whether insurance companies ought to reimburse families for GH treatment of a non-GHD child through analysis of: (1) how companies generally make reimbursement decisions, (2) which issues ought to be considered in the context of GH therapy specifically, and (3) the main arguments for and against insurance reimbursement in this context.

How Are Reimbursement Decisions Made?

Reimbursement decisions are not made by a uniform process: every insurance company itself makes the decision about whether to reimburse a particular service. The Health Insurance Association of America (HIAA), the trade organization of

commercial health insurance companies in this country, does *not* make specific recommendations concerning what services should be covered. Rather, it researches some subset of procedures and therapies and disperses this information to member companies in the form of "technology assessments." Each company itself then makes the decision regarding coverage. It is assumed that there are many medically appropriate ways to respond to various conditions, and different insurance "products" at different prices are offered to consumers that reflect this assumption.

Generally, if a service is part of established medical practice, it will be reimbursed. If it is not part of established practice — as is the case with GH therapy for non-GHD children — there is no predicting whether insurance companies will cover the therapy. Nor is it known what grounds companies will use to define a therapy as experimental or conventional. In making the decision, the medical director of a company may consult a variety of sources, including the relevant medical literature, the "technology assessments" available from HIAA, studies conducted by other organizations, medical experts in the relevant field, or medical directors of other insurance companies.

In addition to the lack of uniformity of coverage among companies, coverage is not necessarily static *within* companies, either. That is, if a certain treatment or procedure is submitted as a claim and the decision is made by the medical director that it is "experimental" or otherwise not reimbursable, the policy holder may appeal and, in certain cases, the company may decide to reverse its decision.

Issues to Consider

In considering whether to reimburse GH therapy for non-GHD children, 2 general issues arise. The first is how experimental the therapy is considered to be, that is, what is known about its efficacy. The second is whether SS is considered to be a "disease" comparable to other diseases for whose treatment companies generally provide reimbursement.

Efficacy considers whether synthetic GH will improve either the growth rate or the final expected height of non-GHD short children. Until the efficacy of providing GH therapy in this context is firmly established, most companies are likely to consider the treatment experimental. Data from studies examining changes in expected height following this type of treatment yield mixed results. One study reported a doubling of the growth rates of 6 of the 7 children studied,[1] while another trial found a 50% increase in growth rate in only 2 of the 10 children studied.[2] Similarly, some investigators suggest that certain identifiable groups of children (for example, those who had lower baseline growth rates) were more likely to respond to treatment,[3,4] while other investigators have not found clinical or biochemical predictors indicating which children are most likely to respond.[5] In one study that followed children longer term, predicted adult height of subjects increased by a mean of 2.8 cm after a mean of 3.6 years, but only 13% of children had final adult heights that were more than 2.5 cm greater than their baseline predicted adult heights.[5] For insurance companies to be expected to reimburse GH treatment for non-GHD children, it is likely that there will need to be greater consensus in the medical community that GH therapy is efficacious.

A second key piece to efficacy in this context, however, is the degree to which the child's emotional well-being improves following treatment. Given that the reason parents typically request this treatment is because they believe their child is experiencing less social acceptance and/or fewer opportunities than his or her taller peers, the appropriate test of efficacy is not simply whether *height* changes following treatment, but whether there is less rejection or enhanced self-esteem as a result of therapy. This, of course, is a saliently different question from whether taller children or adults *generally* have greater opportunities and/or acceptance than their shorter peers. Efficacy defined in this way has not been well studied, although one survey of adults who had been treated with GH when they were children found that the adults still had greater psychosocial difficulties than their peers.[6]

The other consideration is whether this type of treatment is consistent with other types of services that companies do reimburse. That is, if GH therapy were demonstrated to be efficacious and therefore no longer considered experimental, is it the "type" of therapy a company would reimburse? As stated earlier, insurance companies are heterogeneous in how they make reimbursement decisions. Medical necessity and consumer demand are phrases that tend to guide the process, but GH therapy (again, assuming it no longer was considered experimental) is exactly the type of treatment that could be decided in either direction. By analogy, for example, reconstructive surgery typically is paid for if it allows for greater mobility or is the result of an accident but not if it is solely cosmetic. Whether GH therapy would be judged as facilitating job performance or as cosmetic undoubtedly would be resolved differently by different companies. Also, companies are more likely to pay for procedures that have a measurable outcome, and self-esteem is not likely to fit into this category, although there certainly is a precedent for mental health services being covered. Again, isolated cases often have served to influence companies to alter their policies.

The Arguments for Insurance Companies Reimbursing Human Growth Hormone Therapy for Non-GHD Children

The main argument for an insurance company's reimbursing for GH therapy for non-GHD children is founded in the principle of justice. If, indeed, GH therapy were shown to be as efficacious for the treatment of non-GHD short children as for GHD short children, then the argument can be made for treating like cases similarly. When a child is short to the point that he or she may be psychologically handicapped, and it has been shown that the psychologic handicap will be improved with the treatment, whether the child is GHD should be irrelevant. If the symptoms,

recommended course of treatment, cost of treatment, and outcome are similar for GHD and non-GHD children, then if treatment for one is reimbursed, so should treatment for the other.

A second argument used for reimbursement is that reimbursement means access, and lack of access means no hope of alleviating a psychologically handicapping condition. Numerous studies have demonstrated that tall people generally are more highly prized in this country than are short people. Similarly, there is ample evidence that tall people experience more career and social opportunities than do short people. However, this is quite different from whether children who were very short for several years have more opportunities and/or improved self-esteem after receiving GH therapy. First, they may not experience enough of a gain in height to be treated by others in a noticeably different manner. It should be remembered that the average change in height achieved in some studies was approximately 1 inch. Thus, it is not a comparison of short to tall people that we ought to be measuring but, perhaps, the difference in how a man who is 5 feet 1 inch is perceived compared with a man who is 5 feet 2 inches. Second, both children and their parents may be disappointed when this medical innovation still leaves the children considerably below average in height. Moreover, by the time treatment is initiated, the children may already have developed their identities, such that therapy could do little to alter self-perception. Again, although the argument legitimately is made that reimbursement, for most people, is the equivalent of access, access cannot be considered the equivalent of improvement until more information becomes available.

A final argument for reimbursement is more general and is founded in the principle of respect for autonomy. It says that individuals ought to have the right to decide which therapies they want in accordance with their beliefs about what will be beneficial to their health. Given the regimen through which GH therapy is given, it is unlikely that there will be a huge ground swell of people coming forth for the injections, and those who do surely are strongly committed in their belief in the potential benefit of the treatment.

The Arguments Against Insurance Companies Reimbursing for Human Growth Hormone Therapy for Non-GHD Children

The main argument currently against reimbursement of GH therapy for non-GHD children is that there are far too many unknowns about the treatment. Studies concerning whether therapy affects the *rate* of growth or final height, whether there are harmful side effects to receiving supplemental GH when one is not deficient, and whether psychosocial well-being truly improves have been inconclusive and have not followed children into adulthood.

However, let us assume hypothetically that efficacy *were* established. There remain several arguments against companies reimbursing this type of treatment. The first is the fear that parents will want to make superchildren out of perfectly normal offspring. The prototypical example is the parent who wants to make a basketball star out of a child whose height falls somewhere in the lower half of the growth curve. The situation may be thought of as analogous to perfectly adequate athletes using anabolic steroids to move their performance into the extraordinary range. This criticism points to the need to be very clear about who would qualify for the treatment, ie, children who, based on identifiable baseline characteristics, are likely to receive benefit from the therapy, not only in terms of increased growth but also in improved self-esteem or other psychosocial measures. Moreover, the therapy should be given only to that fraction of the population whom the medical community consensually determines to be of truly disabling stature. This is very different than having the hormone available for those who simply would like to be taller.

Another reason given for denying reimbursement is that this type of therapy is more "cosmetic" than medical, and insurance companies tend not to cover other elective, cosmetic procedures. Certainly, as stated above, prescribing GH therapy for children who fall within normal ranges but who just want to be taller clearly is cosmetic. Indeed, GH therapy for *all* children is cosmetic in the sense that it changes *appearance* rather than alleviating pain, reducing risk of disease, or increasing life expectancy. What might convince companies to reimburse for children whose height falls below the 1st percentile, however, is a belief that, like plastic surgery following an accident, the treatment places the person in the "normal" range of human appearance rather than taking them from the normal to the extraordinary. Nonetheless, it must be acknowledged that in approving this therapy, some endorsement is being made of values and pressures that say that variations from the normal will be scorned.

A final argument against reimbursement, exactly opposite of the autonomy-based rationale *for* reimbursement above, is that individuals do *not* have the right to decide to which therapies they are entitled. The purpose of insurance is to restore individuals to health or, in some cases, to prevent disease. Moreover, the process by which services are considered reimbursable is by careful attention to what most medical professionals would consider reasonable treatment for a condition; it is not in response to what a policy holder decides he or she wants.

Conclusion

GH therapy is offered as a potential benefit. The only reason not to simply award it is its potential physical harms — the unknown risks of giving GH for a period of years to a child who is not GHD — and psychologic harms — exacerbation of a negative self-image by injections given to alleviate a perceived "inadequacy" as well as the disappointment that may ensue from realizing that, after years of treatment, relative SS remains. Finally, we must consider economic harms — the average cost

of treatment is $20,000 a year, and treatments can last anywhere from 1 to 5 years — something that can be justified only if the benefits are proven to be quite significant.

The question, then, is which way to err. Certainly, reimbursement cannot be expected until more extensive studies examining the long-term efficacy of GH therapy have been conducted. Moreover, it is important for us to continue to scrutinize reimbursement decisions in order to see if they reflect our social priorities. However, if efficacy is demonstrated, and if we continue to categorize therapy for GHD children as a reimbursable service, then those non-GHD children who are equivalent in stature to GHD children and who are equally likely to respond to the therapy ought to be entitled to reimbursement by insurance companies for GH therapy.

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DISCUSSION IV: A

A: Growth Hormone Therapy for Children Who Are Not Growth Hormone Deficient: Should Insurance Companies Pay for the Treatment? - Nancy Kass, ScD

Moderated by Norman Fost, MD

WEISBARD: We can cite examples in American health care where disease is neither necessary nor sufficient for insurance coverage. However, where treatment is provided by physicians for a condition that we are prepared to call disease, coverage is generally presumed when the treatment passes beyond whatever we define, however problematically, as "experimental." If treatment does not fit that criterion, coverage is likely to be problematic *unless* there are other political forces operating. We could then examine what those forces might be, and how they might apply in the growth hormone context.

WIKLER: What is the role of competition for insurance companies? When I have asked insurance executives why a service is offered, they say, "We cannot compete if we do not offer it, because the competition makes it available." Otherwise the insurance companies will offer certain services as a marketing tactic to draw in the kinds of insureds they seek. For example, the insurance company will sponsor a sports fitness clinic to provide advice about what kind of running shoe to purchase based upon the logic that the clinic attracts runners and they (athletes) do not get as sick as often. Insurance companies will offer very elaborate fertility and obstetrical packages because this brings in young families. While these insureds will have childbirth expenses, they do not incur the usually greater expenses associated with more long-term care necessary in old age. So I wonder whether GH therapy may be caught up in the same kind of crossfire.

The other external factor is the desire of the employer. Insurance executives have told me, "We don't really determine what to offer. The employers determine it. We sell packages to companies where the company determines specifically what items and services they want covered, and we then agree to create a package to meet their specifications. The process is based upon what the employers believe they need to offer their employees to keep them happy, and so on."

KASS: You're certainly correct that multiple forces guide the insurance market. It must be remembered that companies are businesses and, as such, market to consumers whom they think will be dependable in terms of paying premiums but who are not likely to pose an unusually high risk of making large claims in the future.

In terms of negotiating with employees, insurance companies do not have an interest in offering particular types of coverage packages *per se*. Rather, they are willing to create whatever types of packages buyers want and are willing to pay for. Employers and insurers are constantly in the process of renegotiating benefits packages and costs. So, to some degree, insurance packages reflect consumer demand. Realistically, unless individuals are confronted with a situation in which growth hormone therapy is prescribed for a family member, they are unlikely to consider coverage for this treatment a priority when selecting or negotiating an insurance policy.

MACKLIN: It has been suggested that a practical approach to entitlement requires that we determine whether a particular condition or disease falls above or below the line of insurability. What does it mean to fall above or below the line when you have no criteria for where you draw that line? I am searching for a rational way to establish this line. You mentioned that Oregon devised an approach based upon preference rankings. I would argue vigorously that mere preferences do not provide a rational scheme nor do they establish a place to draw the line. A preferential ranking system is arbitrary, whimsical, capricious, and subjective. We do not have to start from scratch with everything, but we must establish baseline criteria to draw the line. One cannot arbitrarily decide that growth hormone therapy falls above or below the line. You must look at GH therapy relative to

MACKLIN: other therapies to rationally decide where the line falls. This decision must have specific criteria upon which it is based.

I recently heard that insurance companies recognize their profits in *life* insurance, and actually incur losses with health insurance. Now if this is the case, one might argue that the system is irrational and requires revamping. And, if we vote to discard the existing system, then we could proceed to argue for coverage of human growth hormone therapy and anything else deemed appropriate for coverage. Perhaps we should consider an approach that will let insurance companies reap profits with life insurance and galvanize the country under a more rational *health* insurance system with a single payor.

BAILY: Blue Cross does not do anything but health insurance, and I do not believe that Blue Cross would like to see themselves disappear. What private insurance would like is the best of both worlds: a system where they insure people who are able to afford premiums for the coverage they choose while the government takes care of everyone else; however, the government must not interfere with the privately-insured sector. This is the Blue Cross perspective.

CHARO: Is the definition of what is "experimental" and what is "therapeutic" a decision made separately among companies or made only by the most powerful and best positioned companies? I have never come across a good definition to distinguish these two terms.

KASS: The distinction between what is "experimental" and what is "therapeutic" seems very arbitrary and subject to consumer demand. If I were taking the role of a patient advocate, I would urge a patient or physician to present all the arguments relating to why a therapy is medically necessary, to look for examples of other companies that provide coverage for the therapy, and to document those insurers' rationale for providing coverage.

FOST: The only definition I have ever been able to come up with for "experimental" is that which insurance companies do not pay for. (laughter)

LANTOS: Why does the pediatric endocrinologist have to certify that a child is eligible for growth hormone therapy? The criteria that we are coming to agree on, (eg, extremely short stature and subnormal growth rate) are not the sort of criteria that you really need 3 years of fellowship training to assess. The necessity that a pediatric endocrinologist has to certify a patient as "growth hormone eligible" before insurance companies will pay for GH therapy seems to be simply a way of rationing growth hormone availability. It also comers the market for endocrinologists.

ALLEN: Most, if not all, of us look forward to the day when the criteria for the administration of growth hormone therapy are *appropriately* restrictive and within an affordable range so as to not unduly stress the healthcare budget. Nevertheless, another tier of restriction or gatekeeping is not necessarily a bad thing. For the last several years, pediatric endocrinologists have had one foot on the GH therapy accelerator and one foot on the brake. We (endocrinologists) keep discovering potentially new indications for GH but have not yet defined a clear end point for treatment. Insurance companies need to know the appropriate criteria for initiating therapy and goals and markers for terminating therapy also need to be designated. Unfortunately however, we have not identified criteria for ending therapy, so growth hormone is a "black box" for insurers. We have alluded to different end points such as height appropriate for genetic potential and within the normal range (or a "nonhandicapping") height. But there is a big difference between these criteria. Currently, the last two years of GH therapy for an adolescent, during which optimal final adult stature is achieved, now costs about $30,000/year. Until we identify more specific and reasonable end points for treatment, the skepticism of insurance companies is understandable, in my opinion.

ACCESS TO TREATMENT WITH HUMAN GROWTH HORMONE: ECONOMIC PERSPECTIVES

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Introduction

Now that synthesis of human growth hormone (GH) has eased constraints on its availability, pressure is growing to expand access beyond the small group of patients currently treated. This paper is about the economic aspects of GH treatment: How much does it cost? How many would be treated? Who would pay for the treatment? And would the treatment be worth the expense?

What Does Growth Hormone Treatment Cost?

Measuring the cost of treating a health condition is not easy. First, the condition must be specified. This paper considers only children who are unusually short, for whatever reason, and receiving GH to make them taller; it does not consider GH use by the elderly or by athletes. Second, the standard of care must be defined: the type and number of physician visits and diagnostic tests, the dosage of GH, the type and quantity of any other required medical services or supplies, and the duration of treatment. These may vary with the age and size of the child and the reason for short stature (SS). Third, unit costs must be estimated and applied to these quantities in order to get an estimate of the direct medical care cost of treatment per child treated. This is problematic in a financing system in which reimbursement levels vary significantly with source of payment, and there are no good data on real resource costs.

In addition to direct medical care costs, there may be mental health-care costs — counseling for family members to determine whether a child should enter treatment and/or to help them adjust if treatment is unsuccessful. Such costs should be adjusted by any savings in mental health-care costs if treatment prevents emotional problems related to SS.

There also will be nonmedical costs. These are usually ignored but may be substantial. A 4-year course of medical treatment that includes extensive testing, monitoring, and thrice-weekly or even daily injections requires at least expenditures of time, and may disrupt the child's and the family's life in other ways (eg, no summer camp or summer vacation because it would interrupt treatment).

Finally, the costs of treating side effects should be considered. This requires forecasting the number and type of such effects and measuring their medical and nonmedical costs.

These information requirements are formidable. They are difficult to meet even for simple conditions with well-established treatment regimens. In the case of GH, the effects of treatment are only partially understood and the standard of care is evolving.

Table 1 summarizes the numbers quoted in the literature on the cost of treatment.[1-6] Total direct medical care cost is usually estimated at $20,000, with most of this amount allotted for the GH; there is, however, one low estimate of $10,000.[4] The duration of treatment mentioned ranges from 6 months—a trial period to see if the child's growth rate responds and treatment cessation if it does not—to 10 years,[5] but the usual duration of treatment proposed is 4 to 5 years. The table assumes 4 years. The number of children who should be treated is particularly controversial, but the table arbitrarily chooses children in the lowest 1% of height distribution.

Table 1: **Direct Medical Care Costs of Human Growth Hormone Treatment**

Annual cost of treatment/child[1]	$10,000 - $20,000
Number of years of treatment[2]	4 years
Total cost/child treated	$40,000 - $80,000
Treatment provided to:	
Lowest 1% of height distribution	
Number of children[3]	37,170
Total annual cost	$1.5 - $3.0 billion

1. Estimated range for annual cost of treatment is derived from references 1 to 6.
2. References 1 to 6 indicate that treatment duration can vary from 6 months to as long as 10 years but is usually in the 4 to 5 year range. An average of 4 years is assumed for the table.
3. Based on total number of one-year-old children in 1989. US Bureau of the Census. *Statistical Abstract of the United States 1991* (111th edition). Washington, DC 1991.

Tallying up these numbers gives an annual cost of $1.5 to $3.0 billion to treat only the shortest of short children. To the extent that these numbers include only the direct medical care costs, they are underestimates.

Are the Numbers Large or Small?

The answer depends on the frame of reference. Compared with the $303.6 billion we spend on defense or the $25.6 billion and $23.0 billion we spend on alcoholic beverages and tobacco products, respectively, they seem small.[7] Compared with total federal and state Medicaid spending on children ages 6-20, $6.2 billion,[8] or the federal allocation to the National Institutes of Health (NIH) for medical research, $6.8 billion,[9] they seem larger. Looking at them a different way, if the total cost were spread over all the households in the population, it would cost each household $16 to $32 per year to treat 1% of children.

Who Should Pay for Expanded Access?

The main sources of payment for health care are private insurance, Medicare, Medicaid, other public programs, patients and their families, and private charity. Table 2 gives the 1989 percentage distribution of expenditures on physician services and drugs and supplies by source of payment.

These numbers are not very useful, however, since the structure of coverage and source of payment vary with factors such as patient age and whether treatment is part of a catastrophic episode. Also, one cannot assume that the entire 1% of children would receive treatment. More than 15% of children under 15 years of age are uninsured[10] and many more are underinsured; their families would not be able to afford the costs of GH, the careful diagnosis and monitoring by a pediatric endocrinologist, and other medical fees. It seems unrealistic to assume that donations of services by medical professionals would fill the gap.

Moreover, it is not reasonable to assume that third-party payers will passively accept the responsibility for the new costs. If they do, private insurance premiums will increase and government programs will cost more. Premiums and government program costs are already rising at an alarming rate. Third-party payers are more likely to react to this new situation by taking steps to avoid these costs.

What can they do? The obvious approach—explicitly exclude coverage of GH treatment, for all patients or for all except those who meet narrow medical criteria for GH deficiency—is actually not very likely. Once a treatment becomes part of the standard of care, third-party payers automatically cover it unless they take specific action to exclude it. Third-party payers sometimes do exclude treatment for certain conditions such as pregnancy and childbirth and procedures such as cosmetic surgery and orthodontia, but such exclusions are the exception rather than the rule. Public and private contracts are generally understood to cover "whatever care is medically necessary, and not experimental." Although second opinions may be required for elective surgery and medical appropriateness reviews are growing more common, individual physicians still play the dominant role in defining what is "medically necessary" and thus third-party coverage.

Of course, there must be limits on coverage or the cost would be prohibitive. Limits do exist, and they can be very restrictive. Rather than exclusions of specific conditions, they usually take the form of exclusions of entire categories of services (medical devices, nursing home care, drugs), restrictions on the amounts of services covered, requirements for cost-sharing, exclusion of care for preexisting conditions, and constraints on who is eligible for coverage.

Table 2: **Sources of Payment for Physician Services and Drugs, 1989 (Percent Distribution)**

			Third Party Payments						
					Government				
Type of Expenditure	Total	Out of Pocket	Total	Private Insurance	Total	Medicare	Medicaid	Other–Federal	Other–State and Local
Physician Services	100.0	19.0	81.0	47.7	33.3	23.4	3.6	1.4	4.9
Drugs and Medical Supplies*	100.0	72.4	27.6	15.7	11.9	—	9.2	0.2	2.5

Source: *Health Care Financing Review* 1990;12:24.

*The total for drugs includes both prescription and over-the-counter (OTC) medications. Third parties pay only for prescription drugs. Assuming that all third-party payments are for prescription drugs, third parties paid for 42.3% of prescription drugs and consumers paid 57.7% out-of-pocket.

These limits often produce results that seem to serve neither fairness nor efficiency. It has been argued that drawing a distinction between children who are "growth hormone deficient" and children who are "genetically short" or short because of medical conditions such as renal failure is unfair, because the distinction is not medically meaningful.[11] Yet the third-party payment system is full of distinctions affecting access that are not medically meaningful. The distinction criticized here actually makes more sense than many others in the system.

If the standard of care plays such an important role in third-party payment, how does a particular treatment become part of it? There is no organized process. The treatment diffuses as a result of individual physician decisions based on the medical literature and personal assessment. As this occurs, there may be attempts to develop a consensus through conferences sponsored by various entities, but these are ad hoc and generally do not focus on issues of cost. New drugs must go through Food and Drug Administration (FDA) review for safety and efficacy (but not for cost-benefit analysis) before they can be sold. However, once a drug is approved for one use, other uses often are developed for it without any formal approval process.

If there is an expansion in the group of patients considered medically suitable for GH treatment, third-party payers will limit coverage temporarily by arguing that the treatment is "experimental." Once this is no longer a defensible argument, the treatment is likely to be covered. If the cost is significant (and it is), third-party payers will probably limit their exposure in ways that are not specific to GH.

In addition to increasing premiums (thus making private insurance even less affordable for the uninsured), private insurers may limit coverage of prescription drugs, drop dependent coverage from employment-related health plans, increase out-of-pocket payments for all care, and make SS a factor in screening applicants for family policies in the non-group policy market. Experience with other expensive-to-treat conditions suggests that small firms may experience prohibitive increases in the cost of their health coverage or outright cancellation if an employee's child receives GH treatment; parents of a child receiving treatment may find it difficult to remain employed or to change jobs.

The public insurance program that will be most affected is Medicaid, the federal-state program for certain categories of the poor, including poor children. In fact, recent federal legislation has greatly expanded the number of poor children who must be covered and has established a schedule for phasing in the new groups over time. Medicaid covers physician visits, laboratory tests, and prescription drugs; and there is a statutory requirement that the program not discriminate on the basis of medical condition. (The much discussed rationing process introduced in the Oregon Medicaid program required a special federal waiver of this rule.) This should mean that most poor children will automatically have access to GH treatment if it becomes part of the standard of care.

On the other hand, Medicaid already consumes an enormous share of state resources and a substantial share of federal resources. Medicaid enrollees already face significant limits on access because of low provider reimbursement rates, quantitative limits on covered care, and other restrictions imposed because of budget constraints. If GH treatment becomes an entitlement for Medicaid recipients and poor children are aggressively treated, the care is unlikely to be funded with new resources but rather with resources squeezed from somewhere else in the program.

To summarize, expansion of the medical indications for GH treatment would lead to increased pressure on a financing system in which rising costs are already a serious concern. It is unlikely that the resources to treat the entire 1% of children would be forthcoming. Moreover, the system's response might well have adverse effects on the availability of care to people with other health-care needs.

Would Expanding Access to Growth Hormone Be Worth the Cost?

One must first ask, "How large are the benefits?" Somewhat to my surprise, the background material for this conference left me unsure that there are any net benefits, even judged by the standards of a confirmed "heightist." It seems self-evident to me, as an economist and payer of taxes and insurance premiums, that *medical treatments should not become part of the standard of care unless there is solid evidence that they produce net benefits for those treated.* This seems especially obvious for expensive treatments that do not save lives.

Of course, the principle is simpler to state than to apply. How does one measure benefits? What constitutes "solid evidence?" Should the standard of evidence be lower for treatments that may save lives or drastically improve the quality of life? Should promising but unproven treatments be available to patients who want to spend their own money on the chance of benefit? Should parents be allowed to choose unproven treatments for their children?

Even after acknowledging the complexity of these issues, it still seems absurd to consider spending millions of dollars on GH without strong evidence that the treatment has a significant probability of raising adult height by a significant amount—and one inch does not seem to be significant enough. It seems difficult to justify the personal cost to the child, let alone the resource costs to the family and society, for only a very small increase in adult height, and even more difficult to justify it for an acceleration in growth velocity in a child whose adult height will be normal but who is a "late developer."

This point made, suppose evidence accumulates demonstrating that GH has a significant effect on height and minimal side effects. Would it then be worth it to extend its use to 1% of children? The answer should depend on what we sacrifice to allocate resources to this end.

On the one hand, we could cut back on alcohol and tobacco or shave a few percentage points off the defense budget and easily pay for GH treatment. On the other hand, we are failing to address a host of medical and social needs many would consider more pressing than the needs of short children because we say we do not have the money. Unfortunately, health and welfare programs seem to be the "marginal expenditures," not cigarettes, alcohol, or defense.

For example, by spending the money it would cost to expand access to GH on the Medicaid program instead, 1.6 to 3.2 million children could be added to the rolls—highly significant given the fact that 8.6 million children under the age of 15 years are currently uninsured.[12] Or the money could be spent moving severely handicapped children closer to normal functioning through special training, rehabilitative care, and high-tech devices—items currently not well-covered by private or public payers. Moreover, since equality of opportunity is the issue, one should also consider expenditures outside health care that influence social opportunities—expenditures on education, nutrition, housing, family support, protection from child abuse, development of better employment opportunities, and so on.

How Should We Decide—and Having Decided, How Should We Make It Happen?

The debate over access to GH highlights the fact that our society has no systematic process for assessing whether the value of a particular medical treatment justifies paying for it on a collective basis. Yet, as health care absorbs a larger and larger share of national resources, it becomes more and more important to set priorities wisely.

The difficulties are formidable, since neither the market nor the existing political process is equipped to handle the task. Yet allowing physicians to set priorities, in the guise of defining medical necessity, also is unsatisfactory. The example of GH illustrates this clearly, because the benefits, if any, are social. Doctors have no special expertise in deciding how valuable social benefits are and what priorities should be established among different kinds of social benefits.

We have, however, only begun to recognize the importance of this issue, and it will be a long time before it is resolved. In the meantime, physicians will continue to have great influence on defining the standard of care and, by extension, the allocation of resources to health-care needs. They will have to determine how to exercise this power responsibly. I hope they will recognize the economic implications of their decisions and take them into account.

For example, it is a well-established tradition in discussions of expensive new treatments for health professionals to argue "if we pay for treatment X (kidney transplants, coronary bypass surgery, GH for children with measured GH deficiency, etc), then we should also pay for treatment Y (heart transplants, liver transplants, GH treatment for all children below a specific percentile of height distribution). Is it too much to ask that the argument be reversed? Pediatricians should look at all the highly beneficial things we do *not* do for children and ask, "How can we think of paying for treatment Y until we pay for prenatal care, immunizations, prevention of lead poisoning, services to the severely handicapped, etc."

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DISCUSSION IV: B

B. Access to Treatment With Human Growth Hormone: Economic Perspectives - Mary Ann Baily, PhD

Moderated by Norman Fost, MD

STABLER: I am impressed that GH deficiency and extreme short stature are somewhat submerged, low-key disorders compared to other childhood disorders. Unfortunately, I have not heard our group actually clarify what it is that is wrong with these children and why we must do something for them. There is no Jerry Lewis Telethon for growth hormone-deficient children. It is not a condition which generates a great amount of sympathy, and no one I know of has ever died of short stature (although people who have that condition may feel like that might happen in other ways). My question is this: How does the visibility of a disorder affect allocation of resources, and how successfully has short stature been promoted?

BAILY: In fact, children with growth hormone deficiency seem to be doing rather well in the system. As a nation, we have not guaranteed basic medical care to about 15% of our uninsured children who have conditions that, while they may drastically affect their quality of life, are relatively

BAILY: inexpensive to treat, but for which these children will not receive treatment.

WEISBARD: A typical methodology is to list 5 or 6 of the least advantageous, most expensive technologies that have been accepted into the system, to proclaim that we are already doing all of these, and then to claim that it would be unfair to deny this new one. In this system, new technologies are presumed innocent unless and until proven guilty. I don't think it's a very rational approach in a time of scarce resources and limited access to more cost-effective and socially compelling health care measures.

Suppose we are considering solely whether growth hormone therapy should be made available for people willing and able to pay out of private resources. Do such private expenditures have an adverse impact on the availability of resources that some would argue should be devoted to higher priority medical needs?

BAILY: If this were an adult treatment, I could support "consumer sovereignty" and allow people to pay directly for the therapy themselves at the full cost. There may be people that feel the expense is justified, similar to cosmetic surgery and certain types of sports medicine treatments. However, with regard to children, we have to determine whether the risk/benefit ratio is acceptable given that children themselves are not to be entrusted with this decision. If GH therapy is a safe and efficacious treatment, then we probably should leave the decision to the parents. And while it is true that rich parents will enjoy access and poor parents will not, there are many other types of considerations that are far more important. I would rather see the insurance system subsidize SAT preparation courses or remedial mathematics training for disadvantaged children than growth hormone therapy to increase stature.

GERTNER: This discussion about allocation of expensive health care resources has not addressed whether the high cost of GH therapy is necessary. U.S. orphan drug laws protect the manufacturers of growth hormone from competition and allow them basically to control supply and demand. Consequently, the price of growth hormone is tremendously high. Does society have the right, or perhaps even an *obligation* to do something about excessive costs for certain therapeutic agents especially where these costs are at least partially due to legislation?

BAILY: That is a good point. We have chosen to finance research and development in the pharmaceutical industry by charging the end user a very high price for the therapeutic agent. R&D is subsidized through the drug patent system and orphan drug laws are simply a refinement of that patent system. Control over the research pursuits is in the hands of the pharmaceutical companies; yet it is sometimes clear that marketing motives are not necessarily compatible with the greatest public welfare. In fact, there are some very good economic and theoretical reasons to argue that the public welfare is not being served once the R&D has been fully realized, when the end user pays a very high price for the product. There is literature on marginal cost pricing available which suggests that pricing should be based on the production cost, because otherwise we unnecessarily limit the extent to which people are able to access the product.

UNDERWOOD: Your statement that the benefits of growth hormone are unclear is a bit global, and, in my opinion, inaccurate. In the treatment of growth hormone deficiency, the benefits are clear. They are becoming clear in the investigational treatment of patients with Turner syndrome, and also in the investigational treatment of children with chronic renal failure. The benefits are somewhat less clear in idiopathic short stature. I believe that the high cost of growth hormone therapy is a blessing, because it is a clear impedance to the widespread use and abuse of growth hormone. The cost factor is, in effect, extending the length of time we are alotted to answer some of the outstanding questions. Almost every day I thank the good Lord that growth hormone therapy is expensive, because I think the ultimate benefit of this therapy is potentially greater than the problem we are discussing today.

BAILY: I wish we could find a cheaper way to address and resolve this problem .

KASS: Saying that it is a blessing that growth hormone therapy is expensive once again points out the irrationality of our medical and insurance systems. If we think that limited access is appropriate, cost is not the best way to impose the controls.

LANTOS: The sicker you are, the harder it is to get health insurance especially if you are currently uninsured. The way insurance companies avoid paying is through the "pre-existing condition" exemption from insurance. I wonder whether short stature could be considered as a pre-existing condition.

KASS: The definition of a pre-existing condition is still somewhat gray. Generally, if the condition is something for which you have previously sought treatment, it will be regarded as a pre-existing condition.

HINTZ: You (Dr. Baily) said that we, as pediatric endocrinologists, have influence on healthcare decisions, but you feel that this should not be the case. You also suggested that we (physicians) all have good motives, but that the *system* is bad. So tell me who you feel should have the majority of influence in the system and describe a "good" system.

BAILY: I do not really mean to say that pediatricians and pediatric endocrinologists should not have considerable influence on how we allocate resources in medical care. What I do feel is that physicians currently have a disproportionately large influence. If we take the normal short stature group, where we are emphasizing psychosocial

BAILY: benefits and equal opportunity, these are not areas that physicians have any special expertise in evaluating. Therefore, it seems that the process should recognize and consider the input of others in addition to the medical profession. The medical profession, however, is the only group that can tell us what the efficacy is in physical terms. There should be societal preferences and values incorporated into whether insurers reimburse this therapy or not.

HINTZ: How do you propose we incorporate these opinions into a national system, and is this rational?

BAILY: We cannot have a perfect national system. All we can do is try to improve the present one. One avenue for improvement would be to institute a universal health insurance plan. The British, Canadian, and Western European systems do a better job of resource allocation. None of these systems could be adopted or incorporated into the United States' system because it is unique; however, I do think that there is room for improvement.

MacGILLIVRAY: Many pediatric endocrinologists are using GH treatment in children who are failing to grow and falling further behind each year. To say that GH therapy is experimental is really incorrect. This is a drug that has been used for 30 years. In spite of tremendous experience with GH, however, we continue discovering new things about it and we are continually reassessing and refining our knowledge and understanding of this powerful hormone.

FOST: "Experimental" refers to the newer, investigational applications of GH therapy. But the point about the feelings is that bad feelings associated with short stature have to be weighed against the feelings associated with being premature, the feeling of being pregnant, the feeling of having a lump in your breast and not being able to go to a physician —in short, these feelings have to be weighed against all the other possible uses for available healthcare dollars.

BAILY: I remember vividly being in an organ transplantation conference and having presented the position which I genuinely believe, specifically, that there are other things that are more important than organ transplantation. A woman stood up and she said, "My daughter is alive because of a transplant and you want her to be dead." I thank God every day that I am not a physician practicing in our present healthcare system, particularly dealing with disadvantaged children, because it would tear at my heartstrings to be unable to treat a child. I do not want to trivialize the difficulties of a child who is miserable because of short stature. But you (endocrinologists) also do not have to see children suffering from some other, more serious disorders. If you recognized both and had to choose only one condition to treat, which would you choose? Recently, I cried watching a documentary about a family whose mother was a crack addict. Concerned neighbors had called the police because her children had nothing to eat. I cried as I watched those children being led away by the policemen. Our society should not let that happen. I have shared this because I feel it is important that you understand that I do not lack emotional contact with the problems of short children; it is simply that I think there are many other problems that we fail to address which are at least as important as the implications of short stature.

ENTITLEMENT TO GROWTH HORMONE

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Introduction

Curiously enough, for all the discussion of resource allocation in health care, there is one issue that has not received the kind of extended analysis it deserves. I am thinking here of the impact of constant medical progress on efforts to devise a just mode of allocation. Consider one simple, popular model of fairness—that of the pie which we try to cut in even pieces so that everyone gets a fair share. That is not a bad model for most purposes. But what do you do when the pie itself keeps getting larger and changing shape from year to year, and when different parts of the pie turn out to have different nutrient value? We have no model for dividing that kind of pie. Yet it is precisely the one we have to deal with in contemporary medicine, which constantly generates new therapies—some good, some poor, and most of mixed value.

Growth hormone (GH) therapy is a pertinent example of the problem. Well before we have devised a political consensus on

the fairest way to allocate even immunization and other older, long-standing forms of preventive medicine to children, we are being asked to decide on a place for GH therapy. Here is a new, costly item that can help some children and that may be wanted by many more (or at least wanted by their parents), but the provision of which as an entitlement would be directly competitive with other needs of children. Should GH therapy immediately be granted equal standing or, to revert to my original metaphor, should the entitlement pie be reshaped to include this new item?

When To Treat With Growth Hormone and Why

For my part, I have little trouble resisting the temptation—for the most part. The phrase "for the most part" is meant to allow an exception for medically classic GH deficiency (GHD). GH therapy should be provided as part of entitlement programs if, after appropriate tests, deficiency is established. What about borderline cases? There is a rule of thumb that could be used in that eventuality: when in doubt, do not treat. What about those cases when there is no GHD but the child is simply very short or has a growth trajectory that suggests he will be very short as an adult? No. Just say no.

Now, this is easy for me to say because I am persuaded by the argument put forward by Drs. Lantos, Siegler, and Cutler in a 1989 article appearing in the *Journal of the American Medical Association*.[1] They contend that GH therapy for non-GHD patients runs up against some serious objections: The risks and benefits of the treatment are unknown; there is no perfectly reliable way to determine which children might benefit; and the treatment itself is relatively burdensome. By contrast, the use of GH therapy for those with diagnosable GHD is efficacious and the burden of the treatment is outweighed by the benefits. To that judgment I would add two further considerations.

First, since "short" is a relative term, and since some percentage of children will always be the shortest children no matter how much GH therapy children as a group receive, it is an inherently losing venture to use this medical therapy to cope with the social disadvantages of being "too short." Ironically, it could work only for some short children under the unfair condition that other short children not gain the same advantage and that those already tall be denied the chance to become even taller. My short child can be helped to become taller in comparison with his peers only by keeping them from becoming taller also; otherwise he is back where he started, at the bottom of the ladder.

Second, to expand the entitlement pie at a time when we hardly know how to divide the present pie, and at a time when many children do not get pieces of even that pie, would seem foolish. Unless we assume an increased budget to compensate for the increased demand on the system created by a new technology—an unsafe assumption these days—the net result of a new technology is likely to be a thinning of services for each child. The same amount of money must now be spread over more services.

Reasons To Deny An Entitlement To Growth Hormone For Non-GHD Short Stature

There are, then, some good reasons to deny an entitlement to GH for nonclinical cases. Yet I suspect it will be hard to hold that line, and I want to examine what kind of response might be prepared for some likely eventualities. We should by now be familiar with two types of arguments that typically emerge to overcome initial obstacles to expanded entitlements. The first argument is that since the affluent will surely be able to gain the therapy even in the absence of diagnosable GHD, it would be unfair to deny a like benefit to the poor. The second argument is that even if in this case medicine is being used to treat what is at bottom a social problem—the deleterious impact of excessive shortness and the resulting social bias and stigmatization—it is done all the time and it would be unfair to draw a line here. Let me briefly examine both arguments.

(1) The poor should be entitled to what the rich can buy. Health care has long been seen as one of those basic human goods to which all should have access. Liberals and conservatives alike will usually agree that money alone should not be grounds to deny needed care; they differ only on the best way of bringing about, and paying for, that outcome. One outcome of this agreement might be called "escalatory egalitarianism": if the rich can buy a medical good, it should in fairness also eventually become available to the poor as an entitlement. While this argument is likely to be far more vigorously deployed by liberals rather than conservatives, even the latter are uneasy about seeing obvious medical benefits denied to the poor and expect the market sooner or later to erase the discrepancy.

Whether in liberal or conservative garb, this argument should be resisted with GH therapy. The only pertinent standards for deciding whether the poor should be entitled to a medical service should be *(a)* actual individual benefit, and *(b)* the seriousness of the need to be met. Since there is great uncertainty about the long-term benefit of GH therapy for nonclinical cases, the fact that some rich people might want to buy it should be seen as irrelevant to the justice of the matter.

Most of us would prefer to be rich rather than poor because we could then, on whatever grounds we choose, buy all kinds of marginally useful or even totally useless but desirable goods. That is no reason, however, for those managing entitlement programs to believe they must do likewise. A higher standard is necessary and reasonable, not one fixed on the usually unlimited appetites, medical and otherwise, of the wealthy. Moreover, simply because some people with disposable income are able to define medical need with greater exquisiteness than others is also no reason for entitlement programs to follow them. The princess who suffered from a pea under her mattress is not the person to entrust with setting general standards of acceptable comfort. In the absence, then, of decisive evidence that shortness is a fundamental handicap to getting on with life—even if it might be harmful in gaining the presidency—the behavior of the rich should be irrelevant to the design of an entitlement program.

(2) If medical treatment can alleviate the harm of social stigmatization, it should do so. One of the great puzzles of our health-care system is how it should respond to those problems whose origins are social rather than directly biologic. On the one hand, it is thought deplorable that the health-care system is left to pick up the pieces of, and somehow put together again, lives and bodies ruined by diseases concomitant with poverty and social deterioration.

Why should it be medicine's job to counteract the stigma of excessive shortness? Is that not in the end much more a social than biologic failure? Yet in a less-than-ideal world, medicine may in fact be the only feasible remedy for some of those evils. It would, therefore, be wrong to wait for Utopia before applying an available medical treatment. Medicine has always picked up the pieces of broken societies. Why should it stop here? The latter argument usually wins the day. That is why, when faced with the potential stigmatization of their short children, some parents will turn to medicine rather than place their hopes in the social transformation of biases about size. They are not dumb in that decision, only realistic. But must medicine go along with them? No, not at all.

Medicine should have its own standards about what falls into its domain. It is right and proper, for example, that medicine should treat those gunshot wounds that result from the illegal drug trade. Even though the wounds do not have their origin in the ordinary biologic failings of the body, there is no other way to repair the injured bodies; and the injuries are undeniably real. But the treatment of shortness as a medical condition is an entirely different matter. The injuries imposed by that condition are, unlike gunshot wounds, of an uncertain kind. They will, for instance, be as dependent upon the response of the short people themselves to their condition as to the social attitudes toward them. Some short people seem to hate their condition while others respond with humor and flexibility, choosing for instance to be philosophers rather than corporate CEOs or the nation's President. If it is the case, moreover, that there will always of necessity be some portion of the population that falls into the lower percentile of height, then there is no ultimate solution to the problem other than a change in social attitudes about height. Nothing can be done biologically to eliminate those in the lowest percentile of height, a logical—not a biologic—limit. By contrast, we know that there are societies, many indeed, that do not have a major gunshot wound problem. There is a problem that can be all but eliminated from a society.

What my comments in general imply should be evident. I do not see a serious moral issue in a two-tier health-care system in general or a two-tier system in allocating GH therapy in particular. Indeed, as medical progress yields one new remedy after another for biologically real or socially constructed maladies, there is all the more reason to have a way to distinguish between that which is imperative for good health and that which falls into a more optional category.

I hope that responsible physicians would not cater to anxious parents worried about the height of their child, but some probably will. It will thus be important to keep before our eyes not only the limitations of GH therapy for nonclinical cases, but also the hazards of medically capitulating to social pressures. As matters now stand, being too short falls in an ambiguous category of social ills—perhaps a real problem, perhaps not.

I believe we should just leave it there. This benign neglect means refusing it the culturally sacred legitimation of medicine as the remedy of choice. If anxieties about shortness become routinely medicalized, we can be sure that the pressures to make GH therapy an entitlement will be irresistible; such is the typical history of these matters. While I am short enough myself to understand some of the problems of that condition, so far as I can make out, it is possible to have a decent society even if some of its members suffer the burden of being too short; it is not a fatal or necessarily crippling condition, either physically or socially. To look to medicine to correct the entire human condition, down to feelings of inadequacy about shortness, is to take it even further down a road it may already have stretched too far. There must be some more serious problems out there to tackle.

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ARE HEALTHY CHILDREN OF VERY SHORT STATURE ENTITLED TO GROWTH HORMONE TREATMENT?

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Introduction

Entitlements originate either in prior agreements or in undeserved inequalities in opportunity for human welfare. Health care in particular is an example of how entitlements derive from one or the other of these grounds. Whether based in agreements or inequalities of opportunity, however, health-care entitlements have their limits. Some of our prospective care is of such great expense per unit of predicted benefit that we refuse to pay the necessary premiums or taxes to fund it.[1] Other care is similarly of too little benefit or too great expense to contribute as much to redressing inequalities in opportunity for human well-being as alternative investments of equivalent resources would.[2] The underlying logic of entitlements, then, also contains the reasons for detecting their limits.

The Case Against Entitlement

I will argue that on neither a foundation of prior agreement nor the ground of unequal opportunity are healthy children of extreme short stature (SS) entitled to growth hormone (GH). Moreover, this holds even for children in the lowest 1% of height distribution. My argument is a moral one, and I will construct it without taking up the debate over the therapeutic merits or scientific facts about GH. I make at the outset a reasonably optimistic set of assumptions about those merits and facts: (1) Use of GH for 4 or 5 years, starting at the proper time, does not risk any harm to the child. (2) Seventy-five percent of the time such use will increase the height of a prospectively 62-inch male by 3 to 4 inches. (3) GH costs $15,000 per year to administer. (4) Of the 75% of extreme SS patients for whom GH is thus physiologically successful, half would not have experienced serious psychosocial adjustment problems because of their SS, and half would have. (5) Of the half who would have experienced adjustment problems, half in turn will find those problems little diminished by their additional 3- to 4-inches of height, while half will be significantly helped, that is, 25% of the 75% who gain height from GH will experience significant psychosocial gain from the treatments. (6) The economic conclusion drawn from these data is that a 3- to 4-inch gain in height costs $100,000, but that a major psychosocial gain costs $400,000. (7) The new members of the subsequent bottom percentile in height will not suffer additional psychosocial problems because others have surpassed them.

Furthermore, I will grant completely, without question, the following conceptual and moral claims: (8) Medical needs are defined by "not only biologic norms but also by personal and cultural values."[3] (9) The lowest percentile of SS children can be considered to have a "handicapping height."[4] (10) It would be inconsistent to treat a non-GH-deficient (GHD) child any differently from a GHD child if both are predicted to grow to the same adult height without GH treatment, and both the same with it. The cause of SS should not matter.[5]

Prior Agreement

One source of entitlements is the prior consent of insurees to contribute enough to a common fund to cover whatever set of services can then be financed. In turn, the proper conceptual framework for setting the limit of the resulting entitlements is not to ask what care people think is warranted despite its cost once they are insured and in need of the care. Once insured, people will of course demand all the care that stands any discernible chance of benefitting them virtually regardless of its cost — others, after all, are picking up all but a relatively tiny part of the tab. Since insured patients have thus lost most of their capacity to estimate opportunity costs (the value of alternative uses of resources), we should address the problem of keeping the use of care within costworthy limits at the *prior point* in the decision process — insuring — when the trouble of medicine's expansion without economic limits fundamentally begins. When subscribers to an insurance pool decide against paying the extra premium to provide coverage for a particular category of care, controlling costs by rationing that care is based ultimately in the will of the very people later denied coverage.

In many cases of congenital illnesses, however, this point gives us little if any ground for limiting the patient's care because of its expense. There is no prior point in time at which a severely ill newborn, for example, can be said to have consented to financial limits on its care. As an individual with even any imagined capacity to consent, the child has never been in a position in which we can in good faith conceive it to be likely to gain by withholding from it high expense-per-benefit care in order to reserve more to devote to it in other respects.[6] In the GH case, however, I propose that we can largely set this problem aside. The child does have a future, even usually a good one, without GH treatments. Furthermore, parents are

faithful representatives of the child's best interest in the decision over whether to insure for GH; the nasty potential conflicts of interest between child and parent are not present, at least not in remotely the same stark degree that they are in many neonatal life-support cases.

I will assume, then, that we can frame the question about agreement-based entitlement to GH treatment in the following way: Would loving, loyal parents choose to invest the extra family resources required by a policy that would cover GH for their healthy children in the lowest percentile for height? That is, given by assumptions stated earlier, would they agree that the significant amelioration of a very short child's psychosocial adjustment problems was worth $400,000? Put it another way: in concert with 532 other couples parenting 1 child each, would they be willing to pay an additional $150 per year for 5 years to significantly help (not just treat) *one* short child? They would thereby gain a 1:533 chance of significantly benefiting their own child.

The first thing we must ask ourselves in trying to answer such a question, of course, is what alternative investments we could make with the money. Those could be either investments in care for other sorts of potential health problems or investments in other things for the very same children who end up in the bottom percentile. For example, what about a $75,000 trust fund (near-term value, which would be much higher by the time the child became an adult) for each of the 5.33 bottom percentile children in the pool? This kind of comparison brings us up in our seats on the GH entitlement issue. I suggest that it is indeed quite clear that almost all of us, as loving and faithful parents, would definitely prefer alternative investments, not GH treatments.

There is no argument for entitlement to GH treatment, then, in either the actual or presumed consent of subscriber parents. In fact, we have in this prior consent foundation of entitlements a convincing argument for precisely the opposite conclusion: *for a typical group of parents and their extreme SS children, GH treatment clearly and definitely ought not to be covered by insurance.* Note, of course, that it does not necessarily follow from this that GH treatment should never be prescribed. If particular parents wanted to purchase it out of pocket or if they had paid for an insurance policy at higher rates that made clear at the outset that the extra payments covered their children for the sort of ultimately psychosocial assistance occasionally accomplished in GH treatments, then their extremely short children might well receive GH treatments.

Unequal Opportunities for Welfare

What does this other basis of entitlements tell us about GH? Should a "height-handicapped" child (bottom percentile) be helped to gain additional stature simply because that is what we owe a person who faces noticeably greater problems in life through no fault of his or her own? We owe roughly equal opportunities for future welfare to each and every individual child, and we would be reducing mildly handicapped children to impersonal items in an aggregate sea of socially efficient benefits if we denied them coverage for GH treatment because its expense made alternative investments more attractive.

But there are 2 nasty questions here for any such argument. First, does extreme SS diminish opportunity for welfare enough to rank its GH treatment remotely close to the next-biggest rectification of less-than-equal opportunity achievable for children in our society? If we are going to use equalization of opportunity arguments, we need to use them consistently. That will get us quickly back to comparisons between what we can do for children of SS with GH and what we can do for other disadvantaged children not yet given a fair shake in our society. Put that way, I fail to see how any hard-thinking group of parents and citizens would ever decide to fund GH treatment for healthy SS in the current United States.

Second, even for height-handicapped children themselves, we must ask how we can best improve likely opportunities for well-being. There is simply no magic here in height or its remedies simply because height is one of the biologic bases from which we then develop personalities and go out and encounter the world. Health care often does get its importance from increasing or preserving a person's whole range of opportunities. But it is by no means unique in that respect (witness education and even certain financial investments), and major parts of health care do not represent future potential and opportunity any more than a variety of other things we desire. The added 3 to 4 inches likely brought about by GH treatments may look like a significant enhancement of some sorts of opportunity for a person whose opportunities are not otherwise hampered much at all. But if someone already faces other significant barriers, or if a person does not value as highly as some others might the sorts of opportunities that taller stature may provide, how can we justify spending *large* amounts of money on children to marginally raise their height?

The concept of a "handicapping height," too, does little work here in isolation from discriminating judgments about how best finally to use our resources to enhance a child's opportunities. Perhaps we have gotten bewitched by a label. Handicaps come in a huge variety of types and degrees, and a handicap per se hardly gives one an entitlement. How much of a handicap is extreme SS compared with other SS (62 inches for a male, say, compared with 65 inches)? Is it the *height* here that is really making the significant psychosocial difference? Even if it is, how might we frankly teach and help people to overcome this handicap without them actually growing taller? Handicaps *per se* do not create entitlements, nor do medical means of diminishing them.

Once this is noticed, we will not shrink from consistently following through our denial of entitlement to GH treatments for very short healthy children to also deny that GHD children are necessarily entitled to GH. In some cases, they probably are, for example, Turner syndrome patients and hypopituitary children, who carry larger disadvantages and will make especially significant gains from GH treatment. In any case, it is not the cause of short stature by itself that makes a difference

morally. If very short, non-GHD children are not entitled to GH treatments, then many GHD children with an equal height prognosis are also not entitled to GH treatments.

Conclusions

Neither the prior agreement of faithful parents nor less than equal opportunities for overall welfare create an entitlement to GH treatments for healthy children of short stature. At current prices and likely benefits of GH, physicians who prescribe GH and insurance companies who pay for it are positively doing the wrong thing. Prescription of GH extracts resources from subscriber parents without their proper prior consent. It also represents a narrow focus on those dimensions of equal opportunity connected only with stature and unquestioningly assumes that "handicaps" and the medical means for overcoming them automatically gain privileged position in the competition for scarce resources. This focus and this assumption are both to the detriment of the larger fight to equalize opportunities.

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DISCUSSION IV: C & D

C. Entitlement to Growth Hormone - Daniel Callahan, PhD

D. Are Healthy Children of Very Short Stature Entitled to Growth Hormone Treatment? - Paul Menzel, PhD

Moderated by Norman Fost, MD

FOST: Suppose there were 2 people whose heights plotted within the first percentile and who, apart from stigma, were both unable to reach the gas pedal in an automobile. Would that change our perception of the problem or would it change our response?

CALLAHAN: Our response, I believe. This is an auto design problem. There is nothing wrong with the individuals.

LIPPE: It seems to me that we have a cultural bias against short people who have received a medical diagnosis. If our job is to make sure that children grow normally, we should be able to treat them.

CHARO: Specific types of functional impairments (eg, being unable to drive or to operate in a standard house, being unable to see over certain things, or to be ineligible for certain jobs) are not simply a matter of social stigma. These problems clearly fall within the definition of "disability," regardless of etiology or origin.

MENZEL: Let consumers indicate their preferences for what they want covered. I am convinced that if we take this approach to clarify entitlements, we will find very, very large numbers of American parents saying, "leave growth hormone treatment off the coverage listing if it costs $30,000 to $40,000 a year for a major psychosocial benefit."

WEISBARD: We need to distinguish more clearly among three concepts that are not fully synonymous. The first is "entitlement," the second, "allocation," and the third is "access." We need not adopt the same policy along each dimension. Another issue we have not talked very much about is the potential use of GH therapy for enhancement, not for those at the very bottom of the height continuum, but for those of relatively normal stature who want (or whose parents want them) to be taller. I suspect few would advocate government subsidy or mandated insurance coverage, but what stance, if any, should society and the medical profession take regarding the use of growth hormone for height enhancement if it is paid for privately? Should this be permitted, or are there reasons to resist this use of GH "therapy?"

MENZEL: If purchasers of growth hormone therapy and physicians think it will work based on plausible medical grounds, then those parents ought to be allowed to purchase it if (— big "if" —) physicians themselves do not let the parent's purchasing ability of that care influence their prescribing habits for patients who, although insured, do not have coverage for GH therapy. If the insureds do not pay explicitly higher premiums to obtain this coverage, it is likely that a cut from the standard types of coverage has been made to offset the expense. As for entitlement: as long as physicians can work within a multi-tiered system and maintain these distinctions, then I do not worry about allowing a parent to purchase this therapy for their child. However, if physicians cannot keep this distinction straight, then we may end up, regrettably in my view, denying this therapy to the wealthy parent who was presumably not hurting anyone.

CALLAHAN: I am concerned about the phenomenon of escalating egalitarianism. Things start out as fulfilling a desire. Once they are established, they become needs, which then proceeds to perpetuate the perception that everyone deserves them. That is the logic of technological progress in our society. It might be very nice if there could be some agreement specifying certain standard deviations above which one ought not to treat.

MACKLIN: I want to understand whether "pathology" plays a role toward enabling us to make moral distinctions or whether pathology has the virtue of mere consistency. Let us go back to Johnny and Billy and assume they are both

MACKLIN: 4 feet 6 inches in height, thus we are not talking about "enhancement" of height. A biological abnormality (failure to produce a sufficient quantity of human growth hormone) enables you to consistently apply this criterion to all others. What would be wrong with using the criterion of predicted adult height? While it lacks the consistency of the biological criterion, it does set a limit and it has the virtue of justice. It seems to be morally superior and perhaps more compassionate to offer therapy that would help both of these children to achieve a height greater than 4 feet 6 inches even though this approach lacks consistency as a criterion to be used without exception.

CALLAHAN: I would prefer to establish moral standards for GH treatment and pose the fundamental question: What is the purpose of medicine and what should a healthcare system try to provide? My answer is that it should correct identifiable biological abnormalities that prevent people from having ordinary species functioning. A healthcare system should not try to satisfy certain human desires such as height preferences.

MACKLIN: Does that include psychiatric illness as well?

CALLAHAN: Yes. A person's mental status affects their quality of life as well as their physical well-being. I would like to be consistent, but if someone presents a convincing argument that certain short children without identifiable biological defects experience psychological distress, and GH therapy improves that condition, I would agree and approve of the therapy; however, the burden of proof remains with that person to prove their position.

ALLEN: Dr. Callahan, upon close scrutiny, many accepted medical interventions designed to correct or detect "identifiable biological defects" do not warrant the allocation of resources.

CALLAHAN: Appendectomy.

ALLEN: What about all the "elective" appendectomies? I am sympathetic to the resource allocation problem in this country, but it is unfair to imply that focusing on the restriction of growth hormone therapy will be a large step toward resolving that problem. The greater problem is the general disenfranchisement of children in our society and by our healthcare system. Funds required to provide adequate healthcare to children are not being made available. If the funds that are now going into terminal care in the last three months of life were redirected to child healthcare, the growth hormone issue would be minor. With regard to the issue of establishing prior agreements (which I do not find very convincing), insurance decisions revolve around the unpredictability of health. There is no way of predicting illnesses to which an individual will succumb. The fact that people may decide that the likelihood of their children having growth hormone deficiency is remote, and thus choose not to access coverage does not necessarily justify excluding coverage completely. If each of us were to analyze our individual policies, we would probably gamble on excluding many of the conditions covered in order to reduce premiums.

MENZEL: I disagree. I think people are foresighted enough to perceive the risks that such an approach would expose them to. I think that this is precisely what insurance is based upon. Your assessment is correct, however, that these decisions should not be made by an uninformed subscriber.

LUSTIG: I think that is untenable, and I will give you an example. What is the deductible on your car for collision?

MENZEL: One thousand dollars.

LUSTIG: The chance that you are going to get a dent in your car is a lot larger than the chance that your child is going to need growth hormone therapy, but you are willing to risk a one thousand dollar deductible in the face of what is likely to happen out on the roads in Puget Sound. It is not that different.

MENZEL: Maybe so, but rational and informed subscribers will not choose to insure for everything, because the cost would be prohibitive. Informed subscribers seek coverage for the conditions/events that have a reasonable cost/benefit ratio. Facts can change my opinion; however, I think it is unlikely that even the most loyal and loving parents of a child with a predicted height (untreated) of 5 feet will determine that an expenditure of approximately $400,000 for a major psychosocial benefit (and the subsequent improvement of final height to 5 feet 5 inches) is appropriate.

CALLAHAN: I agree with Dr. Allen that our priorities regarding the healthcare of children are misplaced; but if you seek to give priority to healthcare for children, you also have to decide which conditions warrant prioritization, with consideration to treatment with very expensive drug regimens versus increased provisions for preventive healthcare and conventional therapeutic options. How does the cost of GH therapy compare with effective prenatal care, assuming funds are available?

ALLEN: In many cases, GH therapy compares unfavorably; however we cannot base these decisions on such a single comparison.

CALLAHAN: Absolutely.

CHARO: I do not agree that healthcare is simply using medical technologies to address medical problems. Medical technologies are tools—tools developed in response to specific medical conditions—which often have applications beyond the specific condition, in that the technology can also relieve the emotional pain and suffering. Why should there be resistance to the transferring of medical technologies outside the medical context?

CALLAHAN: The first problem is to decide what will fall into the domain of the available allocation. One possible criterion would be a biological abnormality or insufficiency

CALLAHAN: that can be managed effectively. If this is the narrow view, then yours is the broad view. If available medical technology can change a situation, is the presence of a biological imperfection really key? I see a problem with bringing medicine in, time and time again, to correct for inadequate social systems. We have implemented medical technology to provide family planning for teenaged pregnancy, which is social pathology, not a medical problem. We compromise our allocation system by allowing so much into the system that even narrowly defined biological disorders do not compete very well. Secondly, we may divert attention from the deeper issues underlying teenage pregnancy. These are some consequences of having a broad standard.

ROOT: I define medicine as "a profession whose charge it is to maintain and restore health and function of the individual to the greatest extent possible." Medicine focuses on the individual. We take care of our patients 1 patient at a time. It is difficult for physicians to consider the broad population when we are interacting with an individual patient and their family.

MENZEL: I empathize considerably with your view of medicine as focusing on the individual, but focusing on the individual does not settle whether having a functional impairment justifies insurance reimbursement of any and every treatment to improve the situation of the person with the impairment. For the boy who is 5 feet tall, whom we hope with treatment to raise to 5 feet 5 inches, the benefit for that individual associated with spending $75,000 may not be sufficient to claim that we are faithful to that individual by prescribing care. I do not see how physicians are really serving the interests of the individual or society by facilitating access to all potential treatments that an insurance company will pay for. Insurance companies ought to be serving the interests of their subscribers, including functionally impaired people, who participate in the determinations of resource allocation.

WIKLER: Here today, the medical scientists are talking about rescuing children who are functionally impaired. But tomorrow, the issue will shift. Because we have a medical means (GH therapy) to achieve a socially desirable goal (to have short children reach a normal height and presumably become achievers as well as social and professional successes), we must have the insurance companies reimburse for this therapy, because insurance companies pay for everything that is medical. Based upon such assumptions, we may have a major social policy problem on the horizon.

JOHANSON: I disagree with your assumption that we can make normal children tall. Since, from clinical studies, GH deficient children who are on average -3.5 SD in height, grow 10-11 cm/year with GH treatment, and non-GH deficient children, who are -2.5 SD in height, grow about 7-8 cm/year with treatment, it is quite logical to assume that normal statured children, ie, 0 SD height, will grow 5-6 cm/year with GH administration. That is a normal growth rate and will not add significantly, if at all, to the already normal height and growth rate. You are not going to change the height of an average size child with the doses of growth hormone that we are using, and much higher doses will dramatically increase the risk of side effects.

ALLEN: None of us are interested in using growth hormone to enhance height beyond the normal range during childhood or adolescence.

HINTZ: But, in 1994, when there are 6 growth hormone companies in the U.S. market—and it costs 10 cents a shot, just like it does for bovine growth hormone . . .

JOHANSON: Somebody will do it, but as I suggested, without very high dosing, which imposes risk, I would expect no benefit.

DIEKEMA: First, endocrinologists choose a specific height percentile cut off because, in their minds, that is the most objective way of determining which children are functionally impaired. The goal of treating children whose heights plot in the lower percentiles is to bring them closer to the 50th percentile—or average—and to correct their functional impairment, not to enhance their stature in comparison to others. Second, the stigma associated with receiving growth hormone injections must be addressed as a potential risk. It is usually parents that are deciding for their child that he or she (the child) is too small, and it is the parents who decide that their child should undergo therapy, a therapy which involves injections. In a child's mind, the perception may be that she is being "treated" because she is, in some way, deficient. This may eliminate any gains in self esteem that might result from an extra inch or two.

TESCH: Whether GH therapy costs $100,000 or $400,000, there is a potential future benefit that is impossible to quantify at this point. No one has data on it, but it is there. We will not know for another 15 to 20 years to what extent these benefits offset some of these costs.

BAILY: In our discussion about functional impairment, I get suspicious when I hear there is a "difference" between men and women. As far as I am concerned, the only thing women do that men do not is have babies, and height does not really influence this ability. I do not think a male of 5 feet 5 inches is functionally impaired, because I am 5 feet 4.5 inches tall. I am also frustrated by the lack of answers from the medical sector to these questions: How tall is tall enough? How tall is the tallest child you want to treat? What medical indications are there to justify treatment beyond simple short stature? I also want to know how tall these children will be, or should be, when they reach their final adult stature.

JOHANSON: How short a daughter would you be happy with?

BAILY: But that's not the —

JOHANSON: Oh, it is, it is!

BAILY: We have already decided that because a parent wants a taller child this does not justify therapy.

JOHANSON: How large of an insurance premium would you pay to make your daughter, who is destined to be 4 feet 6 inches tall, a little bit taller?

STABLER: We keep talking about height and stature, but when you look at the research on how much height contributes to what we call self-image and self-esteem, it is a very small percentage. However, an extraordinarily large number of these short kids have developmental impairments relating to academic and behavioral functioning.

LUSTIG: I would suggest that treating only the physical symptomatology of a child with these types of developmental impairments is not going to solve the problem.

STABLER: We do not know.

Session V:

SUMMING UP: A DEBATE REGARDING POLICY PROPOSALS FOR ACCESS TO GROWTH HORMONE

Editor's comments: It is clear that more complete data, obtained through prospective controlled trials, are needed to address issues of GH toxicity and efficacy in the treatment of non-GHD children. However, while current expectations for GH may be exaggerated, the prospect that GH will prove only to have toxicity without efficacy seems unlikely. For several reasons, discussions of the ethical use of GH should proceed while such studies are in progress.

First, determining what *can* be done with GH is not the same as determining what *should* be done. Successful clinical trials with GH will create demand, and objective thinking about *responsible* GH allocation inevitably will be compromised when pressures of parental demands, profit, and other self-interests arise. Second, GH use should be directed toward goals deemed important enough to justify the necessary allocation of resources. There is currently no consensus about precisely what these goals are. Third, due in part to heterogeneity in responsiveness among diagnostically related groups (eg, Turner syndrome and chronic renal failure), clinical trials alone are unlikely to provide complete answers to the questions of who is entitled to GH and for how long.

In this session, two divergent views of entitlement to GH are discussed. This conference was not a consensus conference, and these presentations are not policy statements. They are, rather, preliminary explorations of medical, ethical, and social issues that need to be addressed to deal rationally and cost-effectively with the likely prospect of expanded GH use.

David B. Allen, MD

WHY GROWTH HORMONE SHOULD NOT BE USED FOR NON-GROWTH HORMONE DEFICIENT CHILDREN

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Introduction and Assumptions

Much of the discussion about the indications for growth hormone (GH) has focused on criteria for the initiation of therapy. While this is a difficult problem, it may be more difficult to determine the endpoint of therapy. Indications for the initiation of therapy may be arbitrary, but at least they can be consistently applied: we can say, for example, that everybody with a predicted adult height below the 1st percentile ought to be treated. Once treatment is begun, however, variations in response to GH therapy and different therapeutic goals will make decisions about when to stop treatment even more contentious than decisions to initiate treatment. I will argue that certain features of GH therapy will make it impossible to limit the use of GH to the shortest children. Instead, we are moving towards a world in which GH will be allocated based primarily on parental preferences. Furthermore, I will argue that pediatricians should resist this trend.

For the purposes of this discussion, I will make 4 assumptions. First, I will assume that there are no long-term side effects of GH therapy. If any major side effect of GH is discovered, it will make treatment of even GH-deficient (GHD) children (and certainly non-GHD children) morally questionable. At present, the practical question is whether, or at what point, we are willing to say that GH is safe. I will assume that evidence of GH safety will continue to accumulate.

My second assumption is that GH will increase final adult height of many non-GHD children. Again, if the data show that this is not the case, there will be no real argument in favor of treatment (except, perhaps, the more limited argument that certain children with growth delay would benefit psychologically by reaching their predicted adult height faster, but I will ignore that issue). The moral argument will center on the use of treatment that is effective.

I will assume that money is not a factor. The money issue too easily cuts both ways. If GH is good for children, it should be provided regardless of cost. If it is not good for children, it should not be provided even if it is free. An intermediate position would be to view GH as a consumer good, rather than a medical treatment, and its allocation based on ability to pay. To do this is essentially to assume that there is no compelling argument for the use of GH in short children and so no serious concerns about injustice. Furthermore, questions of economics and justice must fix a price for GH in order to compare its value with other goods. But the price is both relative and variable. Therefore, it is justifiable, for the sake of argument, to set it very low, so that it drops out of the moral equation. By ignoring economics, I will better focus on the primary question of whether GH is good or bad for children. Only after that question is answered can we discuss its relative worth.

Finally, I will assume that GH therapy will require daily injections for years. In the final part of the paper, I will discuss the implications of any change that would allow oral or transdermal administration of GH.

Short Children Are Healthy

Arguments about whether short stature (SS) is or is not a disease generally focus on the difference between social and biologic conceptions of disease. Such arguments turn on whether something must have a biologic substrate or explanation before it can be classified as a disease. Generally, arguments about the relative contributions of biology and sociology to the classification of an entity as a disease ignore or abjure the idea that there is a thing called health. I believe that health is a nonarbitrary quality that may be present or absent in all living things. Although I cannot define health in a way that is precise and inclusive, I believe, along with Kass, that health is not relative but that it is "a state or condition unrelated to, and prior to, both illness and physicians."[1] Health is not social or cultural, and is not defined in relation to others. It is a property of biologic entities.

In spite of the fact that people who are short may suffer as a result of their stature, just as amputees may suffer as a result of their disability, they are generally healthy. Most of the bad outcomes associated with SS, such as poor self-esteem, poor school performance, lower earning potential, etc, may lead to poor health but are not themselves inconsistent with health. Healthy people may not do well in school or may be poor, but this does not indicate that they are diseased. We generally do

not give otherwise healthy children shots to improve their school performance or improve their earning potential; we give them better teachers and a better education.

The lack of association between stature and health has important implications for the role of pediatricians in dealing with SS. Because stature is not associated with health, there is no height below which we can call someone intrinsically unhealthy, and no height above which we can define someone as being healthy enough. Whatever goods come from height are relative. Generally speaking, the more height one gains, the more such goods will come. Thus, anybody who would want treatment to achieve some gain in height would likely want as much such treatment as possible.

Treatment of Short Stature: The End Point Dilemma

Suppose we see 2 sisters in a clinic — one has a predicted adult height of 152 cm (5 feet 0 inches; just below the 5th percentile) and a growth rate of <4 cm/yr. The other has a predicted adult height of 155 cm (5 feet 2 inches). We treat the first but not the second. At the end of a year of therapy, the first has responded with a growth spurt and now has a predicted adult height of 156 cm. The second still has a predicted height of 155 cm. Do we continue to treat the first, in order to make her 165 cm? Do we stop treatment, since her predicted adult height is now in the normal range? If we continue to treat the first child, do we offer treatment to the second child, since her predicted height is now less than the child whom we are treating? Suppose GH works even better, and after 3 years, our treated child now has a predicted height of 168 cm. Do we continue treatment, or do we say that it has been too successful and so is no longer justifiable?

Such decisions will be manageable if GH hardly works at all, so that the first child moves only from a predicted adult height of 152 cm to 155 cm. If it works well, so that we can titrate doses to allow almost anyone to reach almost any height, we will create unavoidable inconsistency in our treatment. We will inevitably care for children who are too tall to meet eligibility criteria for the initiation of GH treatment but whose predicted adult height is shorter than that of children who are being treated and who are responding. If these children are not candidates for GH therapy, their SS will be relatively more significant, and any psychosocial sequelae of SS will be worsened. If they are treated, it will create a continuously sliding scale of eligibility that will eventually include children of any height.

This dilemma leads to an allocation paradox governing GH therapy for non-GHD children.

> Let p = the final adult height that we consider to define disability, and thus to justify treatment.
>
> Let n = the number of inches above one's predicted adult height that GH will allow one to grow.
>
> Then, either p + n = p , the new height cutoff of children who will have to be considered candidates for GH therapy if GH is to be used consistently (and we would have to revise the formula to be p + n = p, etc . . .). Or, we will be treating people with a higher predicted adult height than people whom we refuse to treat.

If we follow this allocation rule, we will eventually be treating anybody who wants treatment, or else arbitrarily stopping treatment once a minimally acceptable height has been reached. It seems unlikely that anyone who was willing to undergo GH therapy in order to be taller would want to stop GH therapy before he or she attained the maximal height that could be safely achieved.

This allocation paradox shows that, to the extent that GH works and confers benefits on children who are treated, the benefits cannot be nonarbitrarily limited to children below a certain height. The response to GH inevitably creates a sliding scale of eligibility by which children of any height will soon be candidates for treatment. Allocation of GH will then reflect either very individualized assessments of the psychosocial consequences of SS, or very imperfect associations between particular heights and particular problems. Since there are very little data on such associations, and no predictive data, parental assessments of the psychosocial sequelae of SS for their child should be considered as reliable (or as unreliable) as physicians' assessments.

The question, then, is whether pediatricians should prescribe GH for any child whose parents want the child to have GH. The stakes for pediatricians in this debate are high. We ask society to recognize us as having the moral authority to speak about what is in the best interests of children. As our part of the bargain, we agree to be so careful and conservative in our assessments of the interests of children that our views and our opinions will be allowed to override the decisions that parents make for their children.

We are granted such power primarily because we have earned a reputation as the guardians of and spokespersons for the well-being of children. The moral regard in which we are held, and society's willingness to respect our views, is conditional. We cannot say whatever we want. We need to base our views on knowledgeable statements about the health of children. I don't think that we can now make knowledgeable and unambiguous statements that the treatment of non-GHD children with GH is in the best interest of any particular child. Furthermore, I think we can say that widespread use of GH will be detrimental to the interests of children as a whole.

The benefits of GH are necessarily relative. Whether SS is conceived of as disease, disability, or normal variant, GH can alleviate the sequelae of SS only by changing the relative height of some children in relation to others. This highlights the difference between SS and ill health. Stature is relative in a way that health is not, and interventions that preserve or protect health are generally beneficial in a way that GH is not. If all children are immunized against polio or pertussis, they are all

better off. If everybody is screened for and treated for anemia or lead poisoning, then everybody will be better off. The general health of the population will improve. But if everybody was treated with GH and if they all responded, then nobody would be better off. The shortest people would still be relatively short. In fact, everybody would be worse off, since in order to maintain their relative state of well-being, everyone would require a daily injection. If only some people are treated or only some people respond, they will be better off in relation to others, who will be relatively worse off.

Seen in this way, pediatricians who administer GH will be either increasing the net burden of medical treatment for children without any compensatory benefit or selectively conferring benefits on some children by creating detriments for others. GH therapy could be unique among pediatric therapies in that it can confer benefits to some children only at the expense of other children.

Conclusions

What, then, is to be done? This is the point in a talk when it is customary to say that we need further research. However, I'm not sure further research, *per se*, would help. It depends upon what type of research. Most current research, which tries to answer the narrow question of whether GH actually increases final adult height is irrelevant. I have argued against GH therapy for non-GHD children assuming research results that would be most favorable to children — that it is safe, effective, and affordable. Even under those circumstances, I argrue that it should not be used for non-GHD children. Any data indicating that it is ineffective and/or has side effects, and certainly any consideration of social justice, would only strengthen these arguments.

Two lines of research might change my conclusions. One would be the discovery of a method of administering GH by mouth. This would minimize the burden of therapy. If, as I've assumed and as research shows, GH remains safe and effective, an orally administered version should probably be sold over the counter, like vitamins. Parents could then decide for themselves whether they wanted to alter their children's height. Another line of research that might change my conclusions would be research delineating a clear-cut association between SS and psychiatric conditions, and a convincing demonstration that GH not only alleviates those problems but also alleviates them more effectively than alternative psychiatric interventions, such as counseling. Such research is not currently being done.

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GROWTH HORMONE THERAPY FOR THE DISABILITY OF SHORT STATURE

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Introduction and Conceptual Guidelines

Limited availability of human growth hormone (GH) once provided a barrier to expanding its use beyond children who were unequivocally GH deficient (GHD). By necessity, strict arbitrary criteria were established to identify classic GHD children entitled to GH. Today, increased availability of recombinant DNA-derived GH has allowed investigation of its growth-promoting effect in short children who do not fit traditional definitions of GHD. Increased supply has created increased demand; more than twice as many children received GH therapy in 1989 and 1990 than in 1985 and 1986 at an average annual cost per child of $10,000.

Advantages conferred by increased height in social, economic, professional, and political realms of Western society are well-documented. Stigmatization and discrimination are shared by *all* extremely short children, whether GHD or not. *If* GH is shown to have growth-promoting effects in non-GHD children and *if* treatment of such children can be accomplished without toxicity, then what ethical criteria should determine entitlement to long-term, invasive, and (currently) expensive therapy? Would it be justified to restrict access to GH based on the diagnosis of GHD? And whatever the indication for GH therapy, to what attained height should GH therapy be considered an entitlement?

Answering these questions requires rethinking of the medical indications for GH therapy. Toward the goal of achieving both controlled but fair access to GH, the following conceptual guidelines are proposed: (1) GH be viewed as a treatment for the disability of short stature (SS) and not for the diagnosis of GHD;

(2) GH-responsiveness, not GHD, be the central criterion for GH treatment; and (3) entitlement to (and reimbursement for) GH therapy be guided by the degree of disability and the degree of GH-responsiveness rather than by a child's diagnosis.[1]

The Continuum of Growth Hormone Secretion: Disease, Potential, and Handicap

The once clear boundary between GHD and GH sufficiency has become blurred. Traditional criteria for the diagnosis of GHD do not identify all children who are GH-responsive. A continuum of "inadequate" GH secretion likely spans classic and partially GHD children,[2] children with delayed growth and puberty, and other poorly growing short children who pass provocative tests but still secrete less GH than their peers.[3] Furthermore, GH *augmentation* therapy in short children with no detectable abnormalities of GH secretion increases growth velocity and, if given for sufficient time prior to puberty, may increase eventual adult height.[4,5]

Arguments emphasizing proven GHD as the primary criterion for GH therapy are often rooted in notions of disease, handicap, or potential. The treatment of disease, "an abnormal condition of an organism that impairs normal physiologic functioning" (*American Heritage Dictionary*, 1985), is one function of medicine. One might argue that GH therapy be confined to those with the "disease" of GHD. Restoration of hormonal equilibrium by supplementing deficient or suppressing excessive levels of hormones is a justifiable, time-honored principle in endocrinology. The GHD child is viewed as more entitled to therapy because something has been taken away that needs to be restored. The American Academy of Pediatrics statement recommending GH therapy only for GHD children concludes with the old adage, "If it ain't broke, don't fix it."[6] But what exactly is "broke" when it comes to SS and GH therapy? This view ignores both the likely, though yet unrecognized, physiologic "defects" that lead to genetic SS and its accompanying psychosocial impairment. Both GHD and non-GHD short children, if they have a disease at all, have the disease of SS.

If the legitimate function of medicine includes the alleviation of handicap, "a disadvantage or deficiency, especially a physical or mental disability that prevents or restricts normal achievement," then the short child's well-being is viewed in the context of his or her interaction with the environment. GH therapy is justified by recognition that extreme SS interferes with normal activities such as driving a car and reaching shelves, as well as competition for jobs, schools, incomes, and mates. After all, preventing handicapping SS is the primary impetus for treating GHD children. Other beneficial physiologic effects occur with GH therapy, but these are of secondary importance. Growth rate and final adult height are the measures by which we judge therapeutic success. Whether burdens associated with SS of a given degree qualify for designation as a handicap is not the central question. The point is that short children of equal height have the same handicap regardless of the cause.

The concept of potential is also invoked to distinguish treatment of GHD and non-GHD children. For some, a GHD child with parents of normal height is "meant," by virtue of genetic endowment, to be taller than the child with familial SS. He or she is entitled to treatment with GH until a height appropriate for the genetic endowment is attained. GH supplementation of the familial short child who appears to be GH-sufficient is "tampering with nature" and outside the proper province of medicine. But this analysis fails, since both children (given an equal height prognosis) are equally unlucky, one by virtue of having GHD and the other by virtue of having short parents. For both, attaining maximum adult height requires "tampering with nature" by providing exogenous GH.

Equitable Restriction of Growth Hormone Therapy

While concepts of disease, handicap, and potential do not distinguish GHD from GH-responsive children with regard to entitlement to GH therapy, it does not follow that *all* GH-responsive short children are entitled to therapy. Resolving that question requires consideration of balancing benefits and risks and asking further questions about allocation of health-care resources.

Response to GH is not an "all or none" phenomenon. GHD children are likely to be *more* responsive than non-GHD children, justifying their preferential treatment as a class. Possible GH toxicity in non-GHD children, while apparently rare, still requires further study. Risks of psychosocial stigmatization also require careful consideration; short, otherwise normal children exposed to injections to promote growth may conclude (with some accuracy) that their bodies are unacceptable in the eyes of their parents and physicians.[7] Statistically significant increments in final adult height may not actually improve psychosocial adaptation, failing a primary objective of GH therapy. Finally, unrestricted access to GH would shift the bell-shaped curve of height upward without changing the handicap for those at the lower percentiles in competing for social, professional, and athletic status.

Assuming that clinical trials of GH in non-GHD children show efficacy with acceptable risk, how might access to GH therapy be equitably restricted? First, the goals in treating SS must be clarified. If the goal is to achieve each child's maximum height potential, GH therapy would (ethically) need to be offered to any potentially responsive short child. Providing GH therapy only to those with documented GHD and treating them until maximal adult stature is reached would be unfair to equally short, non-GHD children who could grow with GH supplementation. On the other hand, if the goal is to alleviate the disability of extreme SS (from any cause), GH-responsive short children should have equal access to treatment until they reach a height no longer considered a handicap.

This latter goal, bringing short children into the normal opportunity range for height, coincides with society's duty to

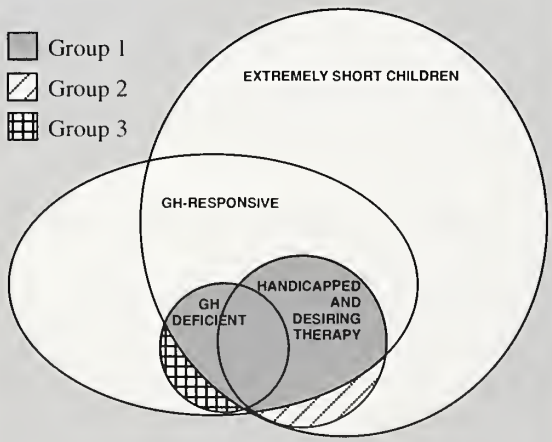
provide basic needs to its citizens. There is no duty to provide the *very best* opportunity for all, and an insistence on equal access to GH by those who have already achieved a normal final height compromises this goal. To improve opportunities for those truly disabled by height, GH must be selectively available to them. The challenge is to define this group, and to apply criteria of disability consistently in deciding when to commence and when to *discontinue therapy*. The diagnosis of GHD should not be rewarded with unlimited access to GH while access is denied to equally handicapped non-GHD but potentially GH-responsive children.

Toward Responsible Use of Growth Hormone

Any definition of "handicapping height" would be arbitrary, but the difficulty in defining boundaries precisely should not be an obstacle to making distinctions. Decisions about treatment are always based on probability, not certainty. While current methods for height prediction remain suboptimal, *some* determination of a height considered a handicap needs to be made if GH allocation in the future is to be both controlled and fair.

Emphasizing degree of disability and GH-responsiveness as selection criteria for therapy equitably fulfills reasonable goals of growth-promoting therapy. (See Figure 1.) Children disadvantaged by stature, regardless of pathogenesis, would be brought closer to or within the normal opportunity range for height. The attainment of maximum height potential would not be a valid treatment goal, and the use of GH to make normal-statured children taller would be opposed. The normal range of height would not be altered, but rather the disparity between percentiles—for example, between the 0.1th and 1st percentiles—would be lessened. By restricting GH therapy to those seeking only to achieve the normal opportunity range for height, we would not exploit the perception that taller is better.

Figure 1: **Allocation of Growth Hormone to Children**



(Group 1) Equitable, but restricted entitlement to GH therapy based upon preferential allocation to children *disabled* by height who demonstrate GH-responsiveness. (Group 2) Children unresponsive to GH or (Group 3) GH-responsive but not sufficiently disabled by small stature, including GH-deficient children who have achieved *non-handicapping adult stature* would not receive public or privately subsidized therapy.

Widespread distribution of GH has been deterred in part by high drug prices[8] and concern about toxicity. Assuming efficacy of GH in increasing final adult height, the relevant question is not how much should be spent on GHD versus non-GHD children but rather how should health-care resources be responsibly and fairly expended on the treatment of SS in general.[9] Resources for this endeavor may in fact be limited, but treatment of severely SS individuals can still be approached with *consistency*. If our goal is to help (all) children attain a height closer to the normal opportunity range, the cause of the SS really should not matter. The central question about allocation of GH is this: To what maximum height should any GH-treated child be entitled to receive private or public support?

Moreover, the crisis in GH allocation will expand not with its failures but with its successes, and not as the cost of therapy rises but as it falls. These impediments, which may be resolved soon, have distracted attention from the issue of responsible use of GH. What we can do with GH therapy is not necessarily what we *should* do. We who prescribe GH should now ask how we would respond if families who do not require insurance reimbursement strongly request GH therapy. Without guidelines for restriction based arbitrarily on likely final adult height, access to treatment would increasingly reflect ability to pay, providing yet another societal advantage to those already well-off. Rather, a consistent goal of growth-promoting therapy should be to lessen the burden for those who are so short as to be handicapped; that is, to provide GH therapy to those disabled by height only until a height within the normal opportunity range is attained. Consideration of degree of disability, rather than diagnosis, both when commencing and when discontinuing GH therapy, will most responsibly contain an expanding cohort of candidates for GH treatment.

The physician's duty to respond to the needs of each child does not necessarily extend to parental aspirations or hopes for the child. In an era of plentiful GH, child advocacy requires consideration of the needs of all children, bringing as many as possible into the normal opportunity range of height without deliberately trying to make some taller than others.[10] The paradox of GH therapy is that no policy regarding its use will ever eliminate the 1st percentile. GH cannot replace parental love and nurturing of a child, regardless of the child's height. Prudent use of GH will recognize these limitations, encouraging physicians to respond to concerns about SS more often with counseling than with injections.

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DISCUSSION V: A & B

A. Why Growth Hormone Should Not Be Used for Non-Growth Hormone Deficient Children - John Lantos, MD

B. Growth Hormone Therapy for the Disability of Short Stature - David Allen, MD

Moderated by Louis Underwood, MD

FRASIER: I am disturbed about the prospect of discriminating against children who have the disease of growth hormone deficiency. We do not only treat short stature, we correct the deficiency as completely as possible. Stopping the treatment of a growth hormone-deficient child before he or she reaches their final height based upon a debate regarding fairness is, I think, ludicrous in the extreme. At the same time, to argue that insurance coverage should not be an entitlement to short children when there is a disease that we are treating is also ludicrous. It is a mistake to lump a disease entity with short stature. I do not think the same rules apply. If a growth hormone-deficient child, when fully treated and fully grown, is 5 feet 10 inches tall, I do not see any reason why the growth hormone therapy should have been stopped when that individual was 5 feet 2 inches tall. If this seems unfair, well, life is unfair.

LANTOS: I agree that this sort of arbitrary selection does not make sense. It creates the worst of all possible scenarios. To set an arbitrary cut-off height seems silly; however, the implications of treating someone who is going to be 4 feet 6 inches tall to reach a height of 5 feet 10 inches, while, on the other hand, denying treatment to another individual who untreated, will reach a final height of 5 feet 2 inches and with treatment could reach a height of 5 feet 10 inches, also does not make sense.

FOST: Doug, there are people who have disorders of heart muscle function, which by anyone's criteria would be considered a disease. If one desired, we could spend half the gross national product and give many quality years of life to these individuals. It does not follow that because we can do it we *should* do it, or that such an approach represents a responsible use of limited healthcare resources.

FRASIER: I do not believe in "Mount Everest" medicine either. We do not treat just because the technology is available, but true growth hormone deficiency is a medical condition that exists affecting 5,000 to 7,000, and by some estimates as many as 15,000, children in the United States alone.

FOST: It is illogical to say that because somebody has a disease which results in a disability, they are *entitled* to whatever treatment will manage or cure the disability.

FRASIER: When a patient comes into my office, it is my job, as a physician, to provide information and access to whatever treatment is available. If I cannot do that, I would choose not to be a physician!

ALLEN: I want to respond to that. I feel that I have provided a valuable service to GH-deficient patients by treating them with growth hormone throughout their life to a height of 5 feet 6 inches. This is a fulfilling response for growth hormone treatment. I do not believe that this person then has a right to demand of their insurance company or of our government the continued payment of $20,000 to $40,000 a year to allow them to acquire additional inches of height just because growth potential remains. That is where we disagree. My goal in GH therapy is to achieve a final adult height which is no longer considered a handicap or a disability. This does not imply compromising the quality of treatment provided to growth hormone deficient patients.

LUSTIG: Dr. Frasier, when you give growth hormone to correct a deficiency, why do you stop when a patient reaches final height? Why don't you continue to treat? After all, you're continuing to replace a deficiency.

FRASIER: At this time, we do not know conclusively that continuing therapy replaces a significant physiological deficit. If there were physiological consequences of that deficiency, then I might continue treatment.

ROOT: I think eventually the answer to that question will be, "yes." I also believe that the aging process will ultimately be impacted or managed to an extent by growth hormone therapy. It makes a lot of physiological sense.

MENZEL: Beside cost efficiency, which justifies prior agreement of payment into the insurance pool, another basis for potential entitlement is that short-statured individuals are truly disadvantaged. You must show that the benefit exceeds

STABLER: the expense of rectifying the inequality and handicap. Given those qualifications, I do not oppose continuing growth hormone treatment for some growth hormone-deficient patients.

BRASEL: It behooves physicians who will prescribe these agents for patients, to track, record, and develop data that will be meaningful, so that in 10 or 20 years we will not be asking the same questions nor be in the position of having put alot of money down a rat hole.

LANTOS: The idea of calling this treatment research rather than therapy is superficially appealing, but unless you define the research question, it is meaningless. No one has presented data on the psychological effects of growth hormone treatment.

STABLER: There is preliminary data from a study of normal short-statured children in which we measured self-concept before therapy. Not surprisingly, these children felt good about their appearance, their school work, their family, and their friendships. Following 12 to 24 months of GH therapy, there did not appear to be any statistical difference in self-concept and, presumably, no clinical difference. This interesting—although unpublished—data supports the notion that these children, who are normal in many ways, do not experience psychological harm because we treat them with growth hormone.

LANTOS: It seems a weak justification for growth hormone treatment that treated children are psychologically no worse off than untreated children. I'd like to see some benefit before I began prescribing it.

CLOPPER: I do not think the relevancy will be limited to a *single* outcome. Potentially, there will be several relevant outcomes.

UNDERWOOD: We have done poorly by identifying the relevant outcome as final adult height, rather than the quality of life during childhood, which contributes to the quality of life during adulthood.

STABLER: One of the best treatments for what we might call body image disorder is counselling. Psychotherapy has a proven track record for modifying and improving body-image disorder.

HINTZ: Much of what we have been talking about is drawing lines. Dr. Allen was drawing a line on the basis of responsiveness. We have talked about drawing a line at –2.5 standard deviations for growth rate or upon the basis of whether the individual is disturbed or not disturbed. All of these lines are fuzzy lines. I think growth hormone responsiveness is a more fuzzy line than peak growth response, –2.5 standard deviations, or annual growth rate. We are merely replacing one fuzzy line—the diagnosis of growth hormone-deficiency—with another fuzzy line.

ALLEN: I agree. Trading one arbitrary criterion for another is a poor choice. However, growth hormone responsiveness is actually the effect that we desire to achieve.

HINTZ: I could argue that the effect we are after is an improvement in final adult height. That is a criterion that we might agree on, but it will take 5 to 10 years to verify!

ALLEN: Agreed. I do not know where to draw the line that determines adequate response, but I do believe that we, the community of pediatric endocrinologists, will need to do this in the future. GH responsiveness is closer to our therapeutic objective than merely raising growth hormone levels in the blood.

HINTZ: That is correct. What I am saying is that your therapeutic view may be philosophically attractive, but it has certain practical problems.

MACKLIN: I would like to identify several propositions on which we seem to sharply disagree. First, pediatricians have an obligation to treat children for measurable growth hormone-deficiency. It is a disease and it is treatable. There is no medical obligation however, to treat extremely short-statured non-GHD children because this is merely a *psychosocial* condition, notwithstanding the fact that it can be a very serious one. Second, one goal of treatment is to achieve a certain height, designated by a cut-off below which short stature is defined as a handicap. In that case we would not distinguish between those who are growth hormone-deficient and those who are not. This contrasts with treating a growth hormone-deficient child long enough to achieve their genetic potential. Do you stop the treatment when you have achieved a "nonhandicapped" height regardless of the fact that the child could grow taller based on his or her genetic potential? I would also like to ask why this is relevant to the ethics issue.

HINTZ: We are doctors. We are not ethicists.

MACKLIN: I want to know why treating to achieve one's genetic potential is more ethically relevant than treating to achieve what is in the best interest of the child.

HINTZ: Why is treating to achieve the individual's genetic potential different from what is in the best interest of the child?

MACKLIN: Let us leave that for a later discussion. We need to consider whether a consistent approach to treating extremely short children is ethically important or not. I have heard several arguments or propositions regarding this issue. Dr. Allen argues that consistency is critically important from an ethical point of view, and he maintains that either equal treatment or nontreatment of Billy and Johnny is acceptable. Others suggest that a consistent approach is not ethically important, but feel that it would not be an injustice to treat

MACKLIN: children (with short stature of similar etiologies) in an inconsistent manner, regardless of the etiology. The fourth point of disagreement appears to involve this group's assessment of the risk/benefit ratio. Dr. Lantos argues against treating both the growth hormone-deficient child and the non-GHD child on the basis of uncertainty regarding the risk/benefit ratio, due to a lack of sufficient data showing benefit and/or the stigmatizing effects associated with daily injections. Others contend that presently there *is* a favorable risk/benefit ratio that justifies GH treatment for growth hormone deficiency and possibly other types of extreme short stature. Now the arguments will continue and these propositions might get lost, but I thought it would be useful to identify them.

UNDERWOOD: I think your points are well taken, but I do not know what to do with them.

MACKLIN: I do not think that you have to do anything.

UNDERWOOD: I am relieved.

FOST: Whether or not a consensus develops in the conference depends in part on how the conference is set up. You have identified several issues for which there may not be a consensus, but there may be consensus on others that are important to identify. For example, there appears to be consensus against treatment of a non-GHD child growing within the normal distribution. Since there are people out there with entrepreneurial instincts, it is important just to point this out, even if nothing else. I would urge that we consider a follow-up consensus conference.

GERTNER: Clearly, there is a tremendous divergence of views among endocrinologists that, to some extent, is being swept under the carpet. I would like to address three endocrinologists. To Dr. Root, I agree that things are still to be considered experimental and that treatment of disabling short stature should proceed and has justification, but only if we add an obligation to do this in academic and research centers where the information on safety and efficacy will be collected and provided to the world as a whole.

GERTNER: To Dr. MacGillivray, I sense the feeling that if a patient was not severely handicapped by size, then we should not be inflicting growth hormone on them. That is an extreme view.

And to Dr. Frasier, I hear an extreme opposite view. In my opinion, I am an average-sized person. When I treat a male child with growth hormone deficiency and he reaches my height, I usually stop treatment.

ALLEN: My argument concerning the treatment of *disabling* short stature is based on the premise that these kinds of policy recommendations be considered only if growth hormone is shown to be safe and effective. I am undecided and unconvinced whether treatment of these youngsters is presently justified.

MacGILLIVRAY: Dr. Allen are you saying there is no distinction between these two groups?

ALLEN: No. One group is growth hormone-deficient, the other group is not, or only partially so. However, when you ask what disability they share, this is not really distinguishable, and alleviating the *disability* of shortness is the main reason for treatment with growth hormone.

CLOPPER: We have focused almost entirely on 1 therapy for extreme short stature. Future conferences could profit by considering the range of therapeutic approaches for extreme short stature, including psychosocial and psychoeducational interventions as well.

BAILY: I knew something before attending this conference: prescribers of GH are not going to be able to level down; they will only be able to level up. Therefore, I was hoping to be convinced that there is real *medical* distinction between nongrowth hormone-deficient children and growth hormone-deficient children. Practically speaking, the history of medicine shows us a therapy already established as standard of practice will not be removed, even if there are good non-medical reasons for doing so.

Session VI:

CONCLUDING COMMENTS

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Clarence Thomas recently testified that he was, apparently, the only lawyer in the United States who had not discussed *Roe -v- Wade* and had no views on it over the course of the last 20 years. This was found to qualify him for sitting on the Supreme Court of the United States. I, unfortunately, have already blown it in terms of *Roe -v- Wade,* but until about 2 months ago I had very little to say about human growth hormone (GH). This was felt to qualify me to sit in on these discussions and share some reflections.

Let me begin with the bottom line. All parties were staggered on several occasions, although I did not count any knockdowns. There were several occasions on which I was tempted to call a technical knockout, but as I went over to confer in each corner, I discovered that the managers of the respective teams could not understand my vocabulary.

We have been through this together and it would be presumptuous of me to announce any conclusions that we have reached as a group—except for one, which is that, in contrast to most conferences and events that I attend these days, at this one I actually learned something. From conversations I have had with my colleagues on the ethics side of the divide, that is a shared perspective. However, some questions have not been entirely answered.

The most fascinating aspect of the conference has been the challenge of communicating across disciplinary divides. There has been some very real frustration over the fact that we have different mental pictures of who it is we are talking about, what the nature of the interventions are, what kind of impact these interventions will have, and what this bodes for the future. One of the benefits of having this kind of conference is to be fairly self-conscious about when we are failing to communicate, about trying to ask our questions more precisely, and about fine-tuning the issues we need to work on in the future.

There was a statement in one of the articles that "in the absence of clearly defined criteria, there is a need to turn to the ethical norm of pediatric practice." Those of us based here at the University of Wisconsin wondered if that was a covert allusion to Norm Fost, the "ethical Norm" we deal with in our daily lives. One of Norm's credos is that good ethics start with good facts. I was struck by the fact that the dominant paradigm and image of our conversations together involved Johnny and Billy and what we are to make of that rather arresting comparison that was put forward in David [Allen] and Norman's [Fost] paper and taken up in our discussions. The hypothetical cases of Johnny and Billy focus attention on the ethical discomfort we have in the lack of seemingly morally relevant differences between these 2 parties and the issue of whether we can justify differences in our treatment approach and the underlying financial approach of entitlement to treatment in these cases. Even given the extremely problematic character of coming to a shared sense of what is meant by disease in this context and how it is evaluated, I will express my own concern about whether the categories of GH-deficient (GHD) and non-GHD children quite capture what it is we want to look to here in a way that is useful.

We seemed to have enumerated four possible responses. There was, in fact, support for each of these positions in the way we think about Johnny and Billy. First is that they are really different and they should indeed be treated differently. This response is rooted in a disease model and a notion that that disease model should drive our moral analysis and our policy. This response seems to be articulated primarily by pediatric endocrinologists understandably committed to existing practice. A second view, expressed in several variations, is that from some important perspectives they may not really be different, that drawing a really compelling ethical distinction between Johnny and Billy is indeed very difficult; nonetheless, we should treat them as *if* they are different even if they are not. That reasoning came from those of us who are concerned about how to fit this case into a broader ethical framework for health-care access and financing in order to develop lines of thinking and rules that could be applied consistently in this and other areas of potentially very expensive health care. Some form of "disease" driven model seemed the only plausible candidate to apply here, even though many people who made that argument (particularly Norman Daniels and Dan Callahan) expressed considerable discomfort in the basis for that. There were also 2 views that these 2 parties cannot be distinguished in any meaningful terms and we therefore have to treat them the same. Some taking that position said, "Since we are comfortable in the established practice of treating one of them as an entitlement, then we should treat the other the same way using a definition of extreme short stature as a handicapping condition affecting

participation in the normal range of life opportunities." Others suggested: "These are the same. They should be treated the same. We should not treat any of them." That summary is a bit frustrating in terms of drawing us toward a consensus regarding a particularly critical issue.

As I understood him, whatever criteria one uses to distinguish "growth hormone deficient" from "non-growth hormone deficient," height was not the only issue. Between those people identified as classically GHD and those individuals of extreme short stature not meeting those criteria, the range of social and psychologic considerations differed significantly. GH therapy might be relevant to those issues, but other interventions might be as effective, or more effective, and more or less cost-effective. If that turns out to be correct, then there may be some interesting reasons to think about GHD and non-GHD individuals as distinct cases calling for distinct responses. That is a bit frustrating for the ethicists among us who want to draw this line in a neater way. That information confounds some initial assumptions and requires additional work to figure out how best to proceed.

We now face the issue of feeding through the mill of social policy these four very different perspectives. Most of the discussion dealt with the term "entitlement," connoting some notion that private insurance and/or governmental programs funding health care should be required to finance these interventions. A near-consensus was heard that, given the burdens on the existing health-care system, it is difficult to provide a morally satisfying justification for giving priority to these treatments, given their expense, the nature of the benefits, the uncertainty of the benefits, and the risks associated with them. That raises the continuing difficulty of doing good for each individual patient while thinking about the larger picture of health care and how GH therapy fits into it. We heard some suggestions of a Bolshevik approach to collapse the entire system as the necessary ground clearing before systemic reform. I do not know that we are likely to resolve this issue.

Let me conclude with a reflection on what I think the bioethicists can bring to the discussion with the pediatric endocrinologists. We know a whole lot less than you folks do about the technical issues of GH. No question about that. I, on the other hand, bring some conceptual equipment that may be useful, a fund of experience with problems that have arisen elsewhere in health-care decision making and from which we may learn some useful things in thinking about this set of problems. A classic case in bioethics was the evolution of the social response to end-stage renal disease and the developing governmental policy on paying for dialysis. That struck me as one of the most compelling metaphors for where we are at in this discussion about GH. At the time, dialysis was an extremely expensive and extremely limited resource. The relevant health-care community, largely consisting of subspecialists at academic centers interested in research objectives as well as the needs of these patients, defined rigid criteria concerning when dialysis would be highly efficacious and when it should be used. We then entered into public discourse and lobbying efforts to persuade Congress to mandate public entitlement and payment for dialysis treatment.

Poignant discussions about empathy and identification with people suffering from a particular condition were very much a part of that experience. As some of you know, the culminating moment involved dialyzing a patient in a congressional hearing room and suggesting to the assembled congressmen that if they did not act, they would be responsible for the death of this individual and many others. It was a very compelling demonstration, but, as we have learned, it is one that can be made on behalf of numerous different causes. The Congress did act. Public funding was provided and we can now look and learn from what transpired. What happened is that the nature of the provision of dialysis changed remarkably. The people offering dialysis services ceased to be largely academic researchers and became commercial enterprises making considerable money in the context of assured government payment. The indications for dialysis, again, expanded beyond anyone's imaginings: people who clearly were believed to be inappropriate candidates in the early days now have to go into the courts to get permission to discontinue treatment when they think it doesn't serve their purposes anymore.

That is the kind of case that gives pause to some of us when we consider where we may be going with GH. There has to be some discussion of motives. I have been extremely impressed with the integrity and thoughtfulness of all the people participating in this discussion. I want to suggest, however, that you may not be the folks making the decisions and putting care into effect if GH therapy is safe and efficacious, and can be of use not just in the fraction of a percent but along fairly broad lines as enhancement therapy rather than treatment for a disease or extreme short stature. Drawing lines to control that will be very, very difficult and articulating rationales for control will be tremendously important. For myself, I am doubtful that anything measured by standard deviations or by percentages, not to say anything expressed in terms of centimeters, will be promising in that regard. And, as Norm suggested, the virtue of holding this meeting early in the development of the technology is that this relatively small group has an opportunity, one that will not present down the road, to initiate the development of professional consensus and standards of professional practice as to what is appropriate and, maybe more important, what is not appropriate use of GH and to articulate the rationale for that policy.

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Growth Hormone Deficient-Like Syndromes and Their Etiologies

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Children with a growth hormone deficient (GHD)-like phenotype but with normal or increased levels of immunoreactive growth hormone (GH) have been reported, beginning with the descriptions of a group of Jewish children by Laron et al.[1] Most of these children with a GHD-like phenotype have low insulin-like growth factor 1 (IGF-1) levels. Some fail to respond to human GH (hGH) injections with increased IGF-1 concentrations,[1] while others respond to hGH injections with increased IGF-1 concentrations and significant increases in growth velocity.[2,3] A few patients with a GHD-like phenotype have normal or increased IGF-1.[4,5]

Since GH acts mainly through its induction of somatomedins or growth factors, mainly IGF-1 and to a lesser extent IGF-2, a derangement of any event in the entire sequence of GH → GH receptor → IGF-1 generation → IGF-1 receptor → post-receptor activation of biochemical processes leads to growth retardation. The purpose of this review is to consider those conditions producing a GHD-like phenotype in the presence of normal or increased GH concentrations.

Possible Defects In GH–IGF-1 Axis When GH Immunoreactivity Is Normal Or High

In Table 1 (page 2), the possible defects in GHD-like syndromes are listed for those patients with (A) low IGF-1 concentrations and (B) normal or high IGF-1 concentrations. In the first group, an abnormal GH structure, a defect in the binding of GH to the GH receptor, or a defect in activation of a post-binding biochemical event at the GH receptor site could produce a low IGF-1 level. In the second group, an abnormal IGF-1 structure, a defect in IGF-binding protein (IGFBP), or a defect in the IGF receptor either in respect to binding or a defective post-binding event could produce a normal or high IGF-1 concentration but a GHD-like syndrome.

Investigation of GHD-like children who have significant immunoreactive GH can advantageously include in vitro radioimmunoassays (RIAs) and radioreceptor assays (RRAs) for GH, determination of the RRA:RIA ratio of GH, evaluation of serum GH with high radioimmunoreactive GH with different monoclonal antibodies, measurement of IGF-1 and IGFBPs

In This Issue

Table 1
Possible Defects Producing Growth Hormone Deficiency-Like Syndromes

	SCREENING TESTS (ABNORMAL FINDING)
A. Low IGF-1 Concentrations	
1. Abnormal GH Structure	1a. Monoclonal Antibody Testing of GH (Variability of GH by Different Tests) 1b. RRA:RIA for GH Using hGH Receptors From Human Liver (↓)
2. GH-Receptor Defect	2. Serum IGF-1 After hGH (No Change)
a. Binding Defect	2a. GHBP (↓)
b. Post-Binding Defect	2b. GHBP (Normal)
3. GH Antibodies Present	3. GH Antibodies of High Binding Capacity in Serum
B. Normal or High IGF-1 Concentrations	
1. Abnormal IGF-1	1. RRA:RIA for IGF-1 (↓)
2. IGFBP Inhibition of IGF-1 Action	
a. In Serum	2a. IGFBP Ligand Binding (↑)
b. In Tissue	2b. IGF-1-Stimulated AIB Uptake (↓)
3. IGF-Receptor Defect	3. IGF-1 Variants (See Text)
a. Binding Defect	3a. Binding in Fibroblasts (↓)
b. Post-Binding Defect	3b. AIB Uptake in Fibroblasts (↓)

LEGEND:

AIB aminoisobutyric
hGH human growth hormone
IGFBP insulin-like growth factor-binding protein
RIA radioimmunoassay
GH growth hormone
IGF insulin-like growth factor
RRA radioreceptor assay

in serum, determination of the RRA:RIA concentration of IGF-1, evaluation of the IGF-1 receptor binding capability for IGF-1, measurement of aminoisobutyric (AIB) uptake to evaluate post-receptor activity of the IGF-1 system, and testing of fibroblasts to evaluate their ability to generate IGFBPs in vitro. Measurement of IGF-1 in serum following GH administration also is useful. Unfortunately, several of these techniques are available only in research laboratories. Nonetheless, the endocrinologist needs to comprehend the possibilities for diagnostic evaluation in GHD-like children. Therefore the types, advantages, limitations, and possible interpretation of the results of each of these laboratory tests are discussed briefly.

Abnormal Growth Hormone Structure

Several suspect cases of abnormal GH structure[2,3] have been reported, including the first reported cases by Kowarski and colleagues.[2] These patients had a very distinctive GHD-like phenotype but elevated serum GH levels. It was thought that they might have GH with normal immunologic activity but deficient biologic activity.[2,3] They had low levels of serum IGF-1 and responded to GH treatment with generation of IGF-1 and increased growth. This suggested a structural defect in the GH molecule or, alternatively, the unexplained need for pharmacologic doses of GH to be present in order to generate IGF-1.[2,3]

Abnormal circulating GH species were reported[2] when researchers utilized RRAs from liver membranes prepared from pregnant rabbits[5] and ^{125}I-labeled hGH. This assay is now regarded as questionable because the rabbit GH receptor differs greatly in its specificity from the human GH receptor. For this reason, GH receptors from a human lymphoid cell line (IM-9 cells) have been used subsequently in the GH RRA.[6] This method has a disadvantage in that the IM-9 cells must be maintained in culture. Also, different batches of IM-9 cells differ greatly in their expression of GH receptors. For these reasons, membranes obtained from the liver of human donors were prepared in our laboratory. These bind well to ^{125}I-labeled hGH. These specific membrane GH receptors

are stable for over 3 years when properly stored and provide reliable assays. Standards are prepared in normal sera with GH concentrations of less than 1 μg/L, which minimizes interference from GHBP. Reliable results can be obtained with sera in which the GH by RIA is greater than 10 μg/L.

Interpretation of the assay requires comparison of RRA with RIA. Because of the combined error in each assay, only ratios of RRA:RIA less than 50% on repeated testing should be considered indicative of a possible GH abnormality. Since development of this assay and with this criterion, no cases of abnormal GH have been recognized. Furthermore, Dr. P. Rotwein, also of Washington University School of Medicine, has not found abnormal GH mRNA in the very short children he has studied. Unfortunately, the patient reported by Kowarski et al[2] was not studied by this method. The one patient reported by Bright et al[3] was tested utilizing a panel of monoclonal antibodies and the liver hGH RRA method, and no abnormality was found.

The patient reported by Valente et al[7] needs to be mentioned. The investigators reported an abnormal GH in a patient with growth failure. After neutral gel filtration of the serum, much of the GH eluted with molecular weights of 45 kd and 85 kd, rather than 22 kd, which suggests the presence of dimers and tetramers. These oligomers were dissociable with 8 molar urea. The molecular defect in this patient was never further characterized. The fact that this patient had a normal serum somatomedin (IGF-1) concentration makes it unlikely that the abnormal circulating GH complexes were related to the growth failure.

In summary, regarding patients with a GHD-like phenotype and low IGF-1 concentration, no conclusive evidence of a defect in GH structure has been demonstrated, although such defects may exist. Theoretically, patients with severe GHD-like syndromes who respond to GH treatment with increased IGF-1 concentrations would best fit into this category.

Abnormal Growth Hormone Receptors

The growth hormone receptor (GHR) is the next critical step in the cascade. The receptor abnormality could be either in its ability to bind GH or in its post-binding signaling. Patients with abnormal GHRs have elevated serum GH and low serum IGF-1 concentrations. Both growth and IGF-1 generation are unresponsive to exogenous GH. Recognition of cases of abnormal GHRs has been greatly facilitated by study of serum GHBP,[8] as this binding protein is derived from the extracellular domain of the GHR. The circulating GHBP is the presumed product of an enzymatic cleavage of the receptor near the cell membrane and usually has been measured by incubating an aliquot of serum with ^{125}I-labeled hGH and separating the ^{125}I-labeled hGH bound to GHBP from the free ^{125}I-labeled hGH by size-exclusion gel chromatography. For this purpose, we have used a 0.9 x 15 cm Sephacryl® 200 column. Specific binding is determined by repeating the procedure with excess unlabeled GH. A correction is made for GH that is present in sera, and the results are compared with those obtained with a normal reference serum. Because there is a progressive rise in serum GHBP during childhood, results must be compared with age-appropriate controls.

A number of simpler methods of measuring GHBP have been proposed. We have used a method in which the ^{125}I-labeled hGHBP complex is precipitated with a monoclonal antibody directed against the extracellular domain of the GHR. Specific RIAs for GHBP are under development in several other laboratories. Such assays would permit recognition of immunoreactive GHBP that might be deficient in its ability to bind GH.

In Future Issues

The Effects of Irradiation on Endocrine Function in Children: Past, Present, and Future
by Stephen M. Shalet, MD

Sleep, GH Secretion, and Short Stature
by Richard Wu, MD, and Paul Saenger, MD

Teratogens and Growth
by J.M. Friedman, MD

Contiguous Gene-Deletion Syndromes
by Frank Greenberg, MD

Fragile X Syndrome: Review and Current Status
by David Nelson, PhD

Current Status of Somatic Gene Therapy
by Fred Ledley, MD

The Relevance of Developmental Genetics to Human Malformations
by Golder Wilson, MD, PhD

The Spectrum of Undernutrition and Poor Growth
by Fima Lifshitz, MD

GHBP is virtually undetectable in Laron-type dwarfism, a condition characterized by elevated serum GH, very low serum IGF-1, and the phenotype of severe GHD.[1] The condition is heterogeneous, with some patients homozygous for GHR gene deletions[9] or nonsense mutations in whom no GHR protein is produced.[10] In other similar cases, detectable immunoreactive GHR occurs. These patients may have simple amino acid substitutions that prevent specific binding of GH. In affected members of one family, a substitution of thymidine for cytosine resulted in serine replacing phenylalanine at position 96 of the GHR.[11] This mutation, however, did not result in decreased GH binding to GHBP synthesized by recombinant methods.[12]

In African Pygmies an abnormality in GHR appears to be present.[13] GHBP in the sera of young Pygmy children is only slightly reduced but fails to rise normally as childhood progresses, so that by puberty, mean values are only 30% of those of normal-statured African controls. This pattern parallels the growth pattern of these individuals, which becomes abnormal only in later childhood and puberty. Although the precise defect responsible for the decrease in GHBP in the Pygmy cannot be identified at the molecular level, a defect in the regulation of the GH gene seems likely.

Many children with apparently normal GH secretion and serum GHBP still have serum IGF-1 concentrations that are 1 or 2 standard deviations (SD) below the mean for chronologic age. In these patients, GH insensitivity seems to be only relative, as serum IGF-1 rises after GH administration and some acceleration of growth velocity occurs. These patients appear to have a sluggish response at the GHR level or beyond. Theoretically, this explanation could be a contributing factor for constitutional short stature. Unfortunately, after GH is bound to the GHR, the mechanism of signal induction across the cell membrane and the mechanisms responsible for the initiation of intracellular responses are poorly understood. Since none of these response sequences are well known, their contribution to impaired growth remains conjectural.

A functional defect in the ability of GH to stimulate IGF-1 synthesis occurs in a dramatic form in kwashiorkor and less markedly in many forms of clinical malnutrition, including uncontrolled diabetes mellitus. Serum GH is elevated but IGF-1 levels are low. Defects in both GH binding and in post-binding events probably contribute.

Acquired resistance to GH in patients who have received therapeutic GH with initial satisfactory responses suggests the development of immunologic resistance. This is readily determined by testing for GH antibodies in serum. The spontaneous development of antibodies to GH without prior administration of exogenous GH remains a potential cause of GH resistance, similar to the mechanism recognized in the development of insulin resistance.

Abnormal Insulin-Like Growth Factors

Abnormalities of the IGF-1 gene or its expression might result in reduced or absent secretion of a functionally impaired peptide with retained immunologic determinants recognizable by RIA. We have screened children with severe unexplained growth failure for this latter possibility by comparing serum IGF-1 concentrations, as determined by a human placental membrane RRA, with concentrations determined by RIA, and Dr. P. Rotwein has looked for IGF-1 gene mutations by endonuclease protection assays. Thus far, no abnormalities have been recognized in this limited survey. It is possible that a severe homozygous defect would be lethal.

Abnormal Insulin-Like Growth Factor—Binding Proteins

Another possible abnormality to account for a GHD-like syndrome with increased IGF-1 is increased concentrations of plasma IGFBPs. Increased IGFBPs are known to be capable of acutely inhibiting IGF action. Most of the plasma IGFs are complexed to IGFBP-3, and normally the concentrations of this binding protein are closely coordinated with the total concentration of IGF-1 and IGF-2. It is not known whether increased concentrations of IGFBPs could sustain inhibition of IGF-1 action, but we know that genetic conditions associated with increased concentrations of transcortin (corticosteroid-binding globulin) or thyroxine-binding protein are not associated with recognized clinical abnormalities of hormone action.

IGFBPs are produced locally by many tissues, and the type and amount of binding protein produced by various tissues differ greatly. Most is known about the secretion of IGFBPs by human fibroblasts. These cells secrete binding proteins into conditioned media, and also retain binding proteins associated with the cell surface that greatly decrease the response to added IGF-1. We

found that fibroblasts of a short girl with elevated concentrations of serum IGF-1 required almost threefold higher concentrations of IGF-1 to stimulate uptake of a model amino acid (α-AIB) than did normal fibroblasts.[14] However, the response of these fibroblasts to IGF-1 variants lacking in binding protein determinants was normal. The conditioned media from these fibroblasts contained greatly increased concentrations of IGFBPs, and there also was increased concentration of cell-associated binding proteins, particularly a 32 kd species that may be IGFBP-5.[15] These observations suggest that local production of IGFBPs might blunt IGF-1 action and contribute to short stature.

Abnormal Insulin-Like Growth Factor 1 Receptors

The last rung in the cascade of GH→ somatomedin→IGF-1 is the IGF-1 receptor. Two patients have been reported with what could be an abnormality of the IGF-1 receptor.[4,5]

Bierich et al[4] reported a patient with elevated GH and IGF-1 concentrations and a GHD-like phenotype with delayed dentition and skeletal age as well as hypoglycemia. Both immunoreactive and bioactive IGF-1 levels were present. Fibroblasts from a skin biopsy specimen taken at 21 months of age were incubated with ^{125}I-labeled IGF-1. Binding was diminished by 50% as compared with controls. The laboratory data regarding this case are not convincing because the method used would not distinguish ^{125}I-labeled IGF-1 bound to cell-associated IGFBPs from that bound to IGF-1 receptors. Earlier, Lanes et al[5] reported a similar patient with a GHD-like phenotype with normal integrated concentrations of GH but elevated IGF-1 levels by RIA, RRA, and bioassay (SO_4 uptake).

To date, no molecular abnormalities have been recognized in the IGF-1 receptor, although several have been observed in the structurally related insulin receptor. IGF-1 variants such as the (des 1-3) IGF-1[16] and the [Q,[3] A,[4] Y,[15] and L[16]] IGF-1[17] permit characterization of the IGF-1 receptor of isolated cells without interference from secreted binding proteins.

In summary, GHD-like syndromes are still difficult to study, but increasingly refined molecular techniques should provide the capability to clarify the pathophysiology or normal physiologic variations that account for these syndromes.

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This new column, which will highlight specific clinical conundrums, is added at the instigation of the editors. How do you explain the findings? Is there a problem? If so, is it 1 problem (adrenal) or 2 problems (adrenal and gonadal - possibly, hypogonadotropism)? You are invited to contribute your thoughts and/or speculate what these unusual findings signify. Please send your thoughts, ideas, and explanations to Dr. R. M. Blizzard, PO Box 386, Department of Pediatrics, University of Virginia, Charlottesville, VA 22908. We will provide a consensus from our respondents in the next issue.

J.H., a 7 6/12-year-old male referred for pubic hair of 1 year's duration, tall stature, HA 10 3/12 without a history of a growth spurt, and obesity and promiscuity, had a negative prepubertal physical examination except for stage III pubic hair, and testes noted to be "very small." The midparental height (183 cm) fell on the 80th percentile for adult males. The BA was 11 years; serum testosterone, <25 ng/mL; 17-OH.progesterone, 265 ng/dL; 17-OH.pregnenolone, 19.7 ng/mL; cortisol, 24 μg/dL; 11.desoxycortisol, 28 μg/dL; and cortisol, 27 μg/dL. All levels except that for testosterone were modestly elevated for age.

At CA 7 3/12 years samples for serum LH, FSH, and testosterone were drawn every 20 minutes from 2200 to 0200 hours. The range of LH values was 4.3 to 5.2 mIU/mL; FSH, 6.9 to 8.3 mIU/mL; and all testosterone concentrations were <25 ng/mL. Corticotropin (ACTH), 250 mg intravenously, was given at 0801 hours. The results were:

	Normal	0800 Hours	0900 Hours
Cortisol (μg/dL)	10 - 20	23	43
17-OH.progesterone (ng/dL)	50 ± 50 SD	242	426
17-OH.pregnenolone (ng/dL)	0.41 - 1.83	19.7	25.5
11-Desoxycortisol (μg/dL)	<120	318	395
DHEA-SO_4 (μg/mL)	24 - 122	148	130
Androstenedione (ng/dL)	31 - 71	70	90

At CA 8 7/12 years, J.H. returned, after being lost to follow-up, with essentially the same physical findings, a BA of 12 3/12 years, and comparable steroid values. Following 10 days of dexamethasone at 500, 500, and 750 μg during each day, all steroid values were suppressed.

At CA 11 7/12 years he returned because of bilateral cryptorchidism. The height was 165.6 cm (HA, 14 6/12 years) and the BA, 13 6/12 years. The testes (2 mL bilaterally) could be brought into the scrotum. Physical examination findings were those of a prepubertal boy with stage III pubic hair. Laboratory values were: 17-OH.progesterone, 88 ng/dL; 11 desoxycortisol, 104 μg/dL; testosterone, 23 ng/dL; androstenedione, 52 ng/dL; DHEA-SO_4, 257 μg/mL; LH, <1.1 mIU/mL; FSH, 2.8 mIU/mL. His lack of sexual development and "effeminacy" reported by the mother prompted a recommendation for depot testosterone administration (50 mg every month).

At CA 12 9/12 years his height was 171.2 cm (HA, 15 1/2 years). He had received only 2 testosterone injections. Twelfth-year molars had erupted. The serum LH was 1.6 mIU/mL; FSH, 4.4 mIU/mL; testosterone, 93 ng/dL; the testes were 2 mL each in volume.

Please assist us in solving this clinical conundrum.

R.M. Blizzard, MD

Growth Hormone Insensitivity: Clinical Spectrum, Regulation of Growth Hormone, and Related Factors

Several cooperative studies were recently presented at a symposium[1-4] in which the clinical and hormonal aspects of growth hormone insensitivity (GHI) were extensively reviewed.

The first of the 4 reports[1] involved a multicentric clinical analysis of 29 patients (14 male, 15 female) with suspected GHI from 11 countries (9 European countries, Saudi Arabia, and Australia), ages 3.2 to 22.6 years. Their heights ranged from +2.6 to -8.9 standard deviations (SD) (mean, -6.0 SD); their weight was +1.2 to -5.2 SD for height (mean, -2.9 SD). Basal levels of GH were extremely variable ranging from 0.8 to 158.2 mU/L, and were detectable in all. In contrast, insulin-like growth factor 1 (IGF-1) was subnormal in all, 20 to 97 ng/mL (mean, 33.6 ng/mL), in comparison with a normal range for age of 120 to 180 ng/mL, and IGF-1 did not increase in response to short-term administration of GH. In this series, some features varied, showing a spectrum of clinical signs of GHI. Micropenis was found in 9 of the 13 males whose penile size was documented.

The second paper[2] details the regulation of GH secretion in 2 of these patients. Their nighttime pattern of GH secretion was pulsatile, with major peaks exceeding 200 mU/L. Their response to 2 sequential bolus injections of GH-releasing hormone (GHRH) in a 3-hour study was strongly positive, with peaks of 512 and 216 mU/L after the first injection, and of 486 and 150 mU/L after the second bolus. In both subjects, serum GH fell to very low levels during an infusion of somatostatin, and there was a rebound following the end of this infusion. This study showed that the normal dual hypothalamic control mechanism by GHRH and somatostatin is preserved in GHI, and that the lack of negative feedback control of GH secretion is at the pituitary level, probably as a failure of the direct inhibition by GH of its own release.

The third report[3] details the clinical and genetic characteristics of 2 large groups of very short patients with GHI living in 2 separate areas of Ecuador (Central America). The morphology of these individuals was similar to that of GHI patients initially described by Laron in Israel and then by others in different parts of the world. However, some differences were observed: the upper/lower segment ratio remained infantile in adult patients, the hands and feet measurements were above the 10th percentile in all, and three quarters of the patients had a limitation of elbow extension. A history of probable hypoglycemia was reported in half of the cases. The genetic studies showed that 1 of the 2 geographic groups (the area of El Oro; 26 cases: 12 males and 14 females) proceeded from a single extended consanguineous pedigree, while the other (the area of Loja; 21 patients: 19 females and 2 males) was probably inbred but not clearly from a common consanguineous origin. The female predominance in the Loja group of GHI patients suggested the possibility of an association between the GHI trait and a trait lethal for male fetuses.

The last paper in this series[4] presents the results of biochemical studies in the Ecuadoran Loja patients and their heterozygous parents, compared with normal-sized, sex- and age-matched controls from the same area. Patients with GHI had markedly reduced serum levels of both IGF-1 and IGF-2 as well as reduced levels of GH-dependent binding proteins, that is GH-binding protein (GHBP) and IGF-binding protein 3 (IGFBP-3). This was in contrast with increased levels of the non-GH-dependent protein IGFBP-2. IGFBP-2 and IGFBP-3 showed an inverse correlation. Moreover, IGFBP-3 correlated positively and IGFBP-2 correlated inversely with the age of patients. The study of heterozygotes did not show such abnormalities except for a slight reduction of IGF-2 that overlapped with normal control values. Thus, no reliable biochemical marker for heterozygosity was found.

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Editor's comment: *Laron-type dwarfism, one type of GHI, is a very rare familial disease, which has been a model allowing important discoveries in the physiology of the GH receptor and in its genetic mapping. The orientation of the reports summarized here is first and foremost clinical, since no such large-scale studies had been possible previously. The investigators show that the main features of GHI are common to all cases, but that individual variations, and the presence of peculiar features in certain cases or families produce a clinical spectrum. The orientation is also biochemical, with one study suggesting that the excess of GH secretion in GHI results from the lack of receptivity directly at the pituitary level and another study demonstrating that all GH-dependent growth factors and binding proteins are dramatically reduced in GHI, with an inversely correlated increase of one non-GH-dependent binding protein. The lack of a marker for heterozygosity detectable by serum biochemistry also is reported. But heterozygosity can be recognized by appropriate DNA analysis when an index case of GHI has been found and studied within a pedigree, as demonstrated by several authors in recent years.*

Jean-Claude Job, MD

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Vitamins in the Prevention of Neural Tube Defects

Recently, a randomized, double-blind prevention trial was completed by the Medical Research Council (MRC) Vitamin Research Group to determine whether periconceptual supplementation with folic acid (one of the vitamins in the B group) or a mixture of 7 other vitamins (A, D, B1, B2, B6, C, and nicotinamide) could help to prevent neural tube defects (NTDs) such as anencephaly, spina bifida, and encephalocele. A 72% protective effect was found for folic acid supplementation; the other vitamins showed no significant effect.

It has long been suspected that diet plays a role in the causation of NTDs, which are among the most common severe congenital malformations. The possibility that folic acid might be important was raised as early as 1964.[1] In 1980 and 1981, 2 intervention studies[2,3] were published in which periconceptual vitamin supplementation was given to women who had experienced a previous NTD pregnancy and were thus at increased risk for another such pregnancy.[2] These 2 studies yielded somewhat equivocal results, but suggested that folic acid or other vitamin supplementation might indeed reduce the risk of recurrence. The MRC group's randomized, double-blind trial with a factorial design utilizing data from 1,195 at-risk pregnancies from 33 centers in 7 countries removes concerns regarding a lack of randomized controls or the introduction of bias. It has thus been concluded that folic acid supplementation can now be firmly recommended for all women who have had an affected pregnancy and that public health measures should be taken to ensure that the diet of all women of childbearing age contains an adequate amount of folic acid.

Wald N, Sneddon J, Donsem J, et al. *Lancet* 1991;338:131.

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Editor's comment: *Definitive results identifying folic acid prophylaxis as an effective preventive measure for NTDs are indeed welcome. Routine periconceptual folic acid supplementation for all women planning to conceive a child should now become standard practice, and it represents a powerful addition to the arsenal of preventive health care.*

Judith G. Hall, MD

Cystic Fibrosis and Congenital Absence of the Vas Deferens

It is well known that most, if not all, male children born with cystic fibrosis (CF) also have bilateral congenital absence of the vas deferens (CAVD). In most studies, the converse has not been observed, as males referred for CAVD have not generally been tested for CF in the past. Because it is now possible to test directly for common mutation of the CF gene, Rigot et al[1] have recently analyzed a group of men with CAVD for carrier status for the ΔF_{508} mutation of the CF gene. They found that 8 of 19 CAVD patients were heterozygous for this deletion. This frequency of ΔF_{508} carriers is much higher than the expected carrier rate for the general population, which is 1 in 25. In addition, all but 1 of the 8 carriers had chronic sinusitis, and 2 patients had abnormal sweat chloride tests.

The results of Rigot et al have been confirmed by Anguiano et al,[2] who found that 12 of 20 patients with CAVD carried confirmed mutations in the CF gene. These patients all had normal sweat chloride tests and no other signs of CF. It must be that the ΔF_{508} mutation is contributing to the CAVD in some way. Perhaps there is still another allele at the CF gene locus that does not cause CF but does lead to CAVD, and the patients in the study by Rigot et al who showed signs of CF represent compound heterozygotes.

In such a population, the risk of having a child with CF would be between 1 in 100 and 1 in 200. In the past, no one with CAVD has been able to father a child, but Silber et al[3] have achieved successful in vitro fertilization with epididymal sperm from patients with CAVD. Thus, as Rigot et al emphasize, their data on the frequency of CF carriers in CAVD males suggest that testing for the CF ΔF_{508} allele should be performed in these men and their partners whenever in vitro fertilization is planned. In addition, the Silber et al[3] plan a detailed study of the offspring of the CAVD patients. The condition does seem to have a genetic basis—many affected siblings have been observed as well as concordant monozygous twins. If a substantial number of the male children of these patients have unilateral CAVD, it would imply that the condition is due not to a sex-linked recessive transfer from mother to son, but possibly to an autosomal dominant gene.

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Editor's comment: *The concurrent development of in vitro fertilization technology and the ability to identify carriers of CF mutations will have, in this case, a twofold benefit. Now that CAVD patients are able to conceive, the CF analysis will allow counseling regarding their high risk for transmitting a CF gene to their children. The mapping of the CF locus, which appears to be linked or identical to CAVD, combined with inheritance studies of CAVD, will hopefully help to identify the mutation responsible for CAVD.*

Judith G. Hall, MD

Erratum:

In *GGH* Vol. 8, No. 1 (March 1992), an error on page 14 incorrectly references Dr. Yarasheski, et al's abstract entitled "Effect of Growth Hormone and Resistance Exercise on Muscle Growth in Young Men." The correct reference is: Yarasheski KE, Campbell JA, Smith K, et al. *Am J Physiol* 1992;262:E261-E267.

Systemic Delivery of Human Growth Hormone by Injection of Genetically Engineered Myoblasts

The ability to deliver recombinant proteins into the systemic circulation could facilitate the treatment of a variety of acquired and inherited diseases. The ideal recombinant protein delivery system requires a cell that is easily isolated from the recipient, reproduced in vitro, transduced with recombinant genes, and conveniently reimplanted into the host. The secreted recombinant protein from these cells needs to gain ready access to the circulation. Such cells need to survive for long periods while secreting the transduced protein product without adversely interfering with body function. Until the possible use of myoblasts was considered and tried in the experiments reported here, the production of stable and physiologic levels of circulating recombinant proteins in normal animals has been relatively unsuccessful. The use of myoblasts may open new therapeutic horizons, as discussed in the 3 presentations from a recent December 1991 issue of *Science*. These articles are abstracted here.

Myoblasts can easily be obtained from muscle tissue, and genetically engineered myoblast cells can easily be returned to muscle without causing damage. This technique was used by Dhawan and colleagues[1] at Stanford University, who introduced a recombinant gene that encoded human growth hormone (hGH) into cultured myoblasts from mice. A modified gelatin (MFG) retrovirus vector was utilized. These cells secreted hGH at levels ranging between 1,400 to 4,600 ng/10^6 cells per day in vitro. These cells were injected into muscle and hGH was demonstrated to be secreted into the serum at increasing levels over an 85-day period. It was demonstrated that hGH can be continuously produced and secreted by myoblasts that are implanted into muscle tissue. The authors state that "this type of delivery system may be useful in the treatment of children with GH deficiency." They also state that "these findings suggest that somatic cell therapy using myoblasts may have application in delivering to the circulation a number of recombinant proteins."

Barr and Leiden,[2] in the same issue of *Science*, published an article entitled "Delivery of Recombinant Proteins by Genetically Modified Myoblasts." They used a plasmid carrying the hGH gene as the vector to insert these genes into the murine C2C12 myoblast cell line. The cultured transfected myoblasts were then placed into the muscles of mice and circulating hGH was measured over a 3-week period. Thus, the results were corroborated in the 2 experiments. Histologic examination of muscle tissue injected with myoblasts demonstrated that many of the injected cells had fused to form multinucleate myotubules.

A concern regarding such injections with a continuous cell line, such as the C2C12 line, is the possibility that these cells have malignant potential. Long-term studies will be needed to evaluate this possibility. In addition, it remains to be determined if this system can be used to produce physiologic levels of circulating proteins in large animals.

In the same issue of *Science*, Michelle Hoffman discussed in an editorial entitled "Putting New Muscle Into Gene Therapy"[3] the potential applications of these techniquess, including the possibility of treating the genetic defects that cause muscular dystrophy and other diseases. Myoblasts do better than the cells used in previous systems because they eventually differentiate and fuse into existing muscle tissue. Hoffman cautions against excessive and premature enthusiasm, however. The results achieved could be different using primary cell lines obtained from the individual receiving therapy, in contrast to the cells used in the mouse experiments, which were from cell lines perpetuated in culture over many years. A remaining unanswered question is: Does one get sustained expression in primary cells? Also, cell lines are probably unacceptable for use in humans because they are too frequently tumorigenic.

In spite of these difficulties, some investigators such as Barr and Leiden are optimistic about the future of myoblasts for gene therapy. Some researchers are projecting their ideas even further into the future, such as the potential to inject DNA directly into muscle cells, a technique pioneered recently by Wolff et al at the University of Wisconsin and by investigators in San Diego.

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Editor's comment: *My editorial comment is simply this: Wondrous innovations in science never cease. The use of myoblasts as protein carriers is only one of many recent scientific innovations, but one that will undoubtedly receive much attention in the future from the readers of* GROWTH, Genetics, & Hormones. *Congratulations to Dhawan, Barr and colleagues for these stimulating ideas and studies.*

Robert M. Blizzard, MD

Uniparental Disomy in Beckwith-Wiedemann Syndrome

Henry et al have demonstrated that 3 of 8 cases of Beckwith-Wiedemann syndrome (BWS), a fetal overgrowth syndrome, are associated with demonstrable paternal uniparental disomy of chromosome 11. Uniparental disomy is a phenomenon in which both copies of a chromosome have been inherited from a single parent, in this case the father, with a concomitant deficiency of the maternal copy. This result was in contrast with 0 of 18 unrelated controls carrying uniparental disomy for chromosome 11. Furthermore, these authors found an overall increase in the frequency of homozygosity for several 11p15.5 markers in 21 cases of sporadic BWS, suggesting that uniparental disomy probably accounts for an even higher proportion of sporadic BWS cases than the 3 of 8 cases of unequivocal paternal uniparental disomy.

Henry I, et al. *Nature* 1991;351:665.

Editor's comment: *Both BWS and uniparental disomy are of particular interest in the field of genomic imprinting. Many regions of the human genome, including the region of chromosome 11 implicated in BWS, appear to be imprinted, ie, they are differentially expressed depending upon whether they were inherited from the mother or the father. Because of genomic imprinting, 2 copies of an imprinted gene from a single parent, ie, uniparental disomy, might result in a strikingly different phenotype than 1 copy from each parent. The results of Henry et al support this theory and demonstrate that uniparental disomy can be associated with BWS, a cancer-predisposing genetic syndrome.*

Judith G. Hall, MD

Growth Prognosis and Growth After Menarche in Primary Hypothyroidism

Pantsiotou et al examined growth data of 20 girls and 9 boys with primary hypothyroidism from the beginning of thyroxine treatment to final height. Bone age (BA) was determined by the method of Tanner. At diagnosis, girls had a mean age of 8.8 years (range, 3.0 to 13.0 years) and a mean BA of 5.4 years. The mean age of diagnosis in the boys was 9.5 years (range, 3.7 to 14.2 years) with a mean BA of 6.3 years. All patients were treated with thyroxine (100 $\mu g/m^2/d$). In girls, the mean height standard deviation score (SDS) for BA before treatment was +0.59. At final height (17.5 years) the mean height SDS for BA was -0.55 ($P < 0.01$). In boys, the mean initial height SDS for BA was -1.6, at final height (16.5 years) this was decreased to -0.87 ($P < 0.02$). All patients, except 1 girl, were below the 50th percentile at final height. The onset of puberty in boys was at age 13.3 ± 1.4 years, or 1.7 years later than in the normal population. The onset of puberty in girls was at 12.4 years, or 1.2 years later than in the normal population. The mean age of menarche was 13.8 years compared with 13.5 years in normal girls. Therefore, the time from the onset of puberty to menarche (1.4 years) in girls with primary hypothyroidism was reduced as compared with that of normal girls (2.3 years). Unlike normal girls, whose growth velocity decelerated markedly with the onset of menarche, the girls with treated hypothyroidism had a mean growth velocity of 5.1 cm/yr during the year after menarche and 4.1 cm/yr during the second year following menarche. Thus, there was a permanent height deficit in treated primary hypothyroid children and the growth characteristics were markedly different from normal.

S. Pantsiotou, et al. *Arch Dis Child* 1991;66:838.

Editor's comment: *The results of this study confirm earlier work by Rivkees et al (*N Engl J Med *1988;318:599-602) who showed that at maturity girls and boys treated for acquired hypothyroidism were approximately 2 SD below normal adult stature. Both girls and boys in that study were somewhat older at diagnosis than those in the present study, and disease duration was longer. No description of growth characteristics was given in the Rivkees et al report, although both studies report that BA advanced at a greater rate than height age in treated hypothyroid children.*

*In an editorial accompanying the study by Rivkees et al (*N Engl J Med *1988;318:632-634), Fisher suggests that the average age at diagnosis of the children in the study may have limited the period of catch-up growth available to them to about 3 years. It is significant that the children in Pantsiotou's study were younger than those in the Rivkees et al report, yet they showed a similar pattern of growth deficit at final height. The significance of growth following menarche is unclear, as it did not contribute (significantly) to these patients achieving a normal final adult height. It is important that pediatric endocrinologists use caution when predicting final height in children being treated for primary hypothyroidism.*

William L. Clarke, MD

Translocation Chromosome Associated With Both Angelman and Prader-Willi Syndromes in a Single Family

The Angelman and Prader-Willi syndromes have been associated with a deletion in the same region of chromosome 15. Almost all cases of Angelman and Prader-Willi are sporadic; thus, it had not been possible to prove unequivocally that a 15q deletion was responsible for the different phenotypes seen in these 2 syndromes. Hulten et al[1] have now reported a translocation chromosome transmitted within a family in which both Angelman and Prader-Willi children are seen.

Other studies have shown that the only apparent cytogenetic difference between patients with the 2 syndromes is that Angelman is associated with a deletion in the maternal chromosome 15q, while Prader-Willi is associated with a deletion in the paternal chromosome.[2] Thus, it has been postulated that these 2 syndromes represent an example of genomic imprinting, the process by which a gene or chromosomal region produces a different phenotype depending upon whether it is inherited from the mother or from the father. Genetic contributions from both parents usually play complementary but sometimes opposing roles, and both are necessary for normal phenotype. In regions that are imprinted, the phenotype produced by a mutation is determined by the sex of the parent transmitting the mutant allele. In the Hulten et al study, the index child with classic Angelman syndrome had a maternally derived unbalanced 15;22 translocation leading to a deletion 15pter→q13. Another branch of the same family had 2 children with Prader-Willi syndrome who had the same unbalanced translocation but of paternal derivation.

The authors note that the unbalanced translocation in the index children was overlooked at first and classified as the typical 15q11-q13 deletion. The detection of this translocation was achieved only through the application of more specialized in situ cytogenetic techniques. The authors stress the importance of obtaining detailed pedigree information and for the cytogenetic reinvestigation of apparently sporadic cases of both syndromes to look for familial chromosomal translocations.

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Editor's comment: *This report further supports the theory of genomic imprinting. The fact that both Angelman and Prader-Willi syndromes occur in a single family and are associated with the same chromosomal translocation provides striking evidence for parent-of-origin differences in phenotypic expression for certain areas of the genome. It seems likely that there are actually 2 different closely linked genes on the 15q11-q13 region, one maternally imprinted and one paternally imprinted, with both deleted by the translocation in this family. However, the mechanism of imprinting is unknown at this time. It suggests other chromosomal translocations may produce 2 phenotypes, depending upon parent of origin. Particular care may need to be given to submicroscopic deletions with translocations.*

Judith G. Hall, MD

Chorionic Villus Sampling Versus First- and Second-Trimester Amniocentesis: An Update

Two large randomized controlled trials comparing conventional second-trimester amniocentesis with first-trimester chorionic villus sampling (CVS) have shown that CVS carries a small but significant additional risk of fetal loss, a higher rate of false-positive diagnoses, and a higher laboratory failure rate.

First-trimester CVS which can be performed as early as 8 weeks of gestation has an advantage over second-trimester amniocentesis, which usually has been performed between 15 to 18 weeks of gestation, in that it allows for earlier prenatal diagnosis of genetic and cytogenetic fetal disorders and, therefore, earlier termination of affected pregnancies. However, the relative safety and diagnostic accuracy of the two methods have been unclear. A 4-year Medical Research Council (MRC)[1,2] trial has just been completed in Europe, following the Canadian Randomized Trial[3] published in 1989, to address questions of comparative risks, diagnostic accuracy, and subsequent malformation rates in the 2 methods.

The spontaneous pregnancy loss associated with second-trimester amniocentesis is 0.5% to 1.0%. The European results indicate that a woman who received CVS had a 4.6% less chance of a successful pregnancy outcome than a woman allocated to second-trimester amniocentesis. In Canada, there was a difference of 1.7% in total loss rates between the 2 groups.

In both trials, these differences related to all losses, spontaneous and induced, among women allocated to the 2 groups. As Garattini's editorial[1] accompanying the MRC report stresses, a complication in making such comparisons is introduced by the different periods of gestation during which the 2 tests are conducted. CVS is performed during a time when higher natural loss rates are expected, while amniocentesis is done after natural loss rates have peaked. Consequently, because both spontaneous and induced losses were regarded as risks of procedure in both trials, a woman choosing CVS during the first trimester had a priori a lower chance of achieving a successful pregnancy than a woman waiting until the second trimester and choosing amniocentesis. In addition, it probably is psychologically easier to decide to terminate in the first trimester, thus adding to the likelihood of the reported outcome for CVS vs amniocentesis.

Congenital abnormalities in infants following CVS also have been reported. Based on a number of studies, it appears that the possibility of some risk of post-CVS vascular disruption at a very early stage of gestation, which might lead to these abnormalities, cannot be dismissed. It is prudent not to undertake the procedure prior to the 10th week of gestation, pending further analysis.[2]

As Garattini also points out, the ultimate accuracy of the cytogenetic results is as important, and in some instances more so, than concerns of safety. In both the Canadian and European trials, accuracy was somewhat higher for amniocentesis than for CVS; in addition, the accuracy of CVS results is more dependent upon the skill of the laboratory conducting the analysis.[1] The primary reason for reduced accuracy of CVS is confined mosaicism, ie, chromosome abnormalities confined to the placental villi that are not found in the fetus. There also seems to be an increased risk of maternal cell contamination in CVS specimens.

Clearly, a prenatal diagnostic approach is needed that is as safe as second-trimester amniocentesis but that can be conducted earlier in gestation, thus decreasing the risk of physical and psychologic complications for women who choose to terminate an abnormal pregnancy. This new approach could be early amniocentesis (11 to 14 weeks). At a recent conference at St. Mary's Hospital in London,[2] the relative merits and shortcomings of this approach were reviewed. Evidence from a number of centers indicates that early amniocentesis produced a fetal loss rate similar to that obtained with conventional second-trimester amniocentesis. However, one series that included 55 cases done before 12 weeks of gestation showed a loss rate of 14.8% for these cases. Also on the negative side, the loss rate after early amniocentesis in twin pregnancies was 8 of 35. Among 1,000 procedures done at 11 to 14 weeks of gestation at Pennsylvania Hospital (Philadelphia, Pennsylvania), 13 cases of minor orthopedic deformities were identified. The impression was that leakage of amniotic fluid might have occurred in a considerable number of women after early amniocentesis. However, on the positive side, the Belfast, Ireland group obtained a lower spontaneous abortion rate and found no congenital anomalies among 880 live-born babies following early amniocentesis.

Lung hypoplasia, possibly secondary to oligohydramnios, also may be a greater risk with early amniocentesis, as the proportion of amniotic fluid withdrawn is greater for early amniocentesis than for second-trimester amniocentesis.[4] A new technique, amniofiltration, whereby amniotic cells are filtered off as up to 40 mL fluid is withdrawn and the filtrate then returned to the amniotic cavity, might reduce the risk of oligohydramnios while increasing the harvest of cells. It remains to be seen whether the increased concentration of chorionic cells in the amniotic fluid in early amniocentesis increases the number of cases of mosaicism detected and the false-negative rates.

CVS does appear to carry a slightly increased risk of both loss of pregnancy and inaccurate results. Thus, these risks must be weighed against the advantage of earlier diagnosis and termination of an abnormal pregnancy when counseling women contemplating CVS. With the advent of high-resolution ultrasound techniques earlier amniocentesis has become a possibility, and may present a viable solution to this dilemma. We all will watch these developments with interest and hope for a safer and more accurate diagnostic procedure that can be performed at an earlier time than previously has been possible.

Judith G. Hall, MD

References

1. Garattini S. *Lancet* 1991;337:1513. Editorial.
2. Meade TW, et al. *Lancet* 1991;337:1491.
3. Rhoades GG, et al. *Lancet* 1989;1:1.
4. Dean M. *Lancet* 1991;338:748. Editorial.

A Difference in Hypothalamic Structure Between Heterosexual and Homosexual Men

The question has long been asked: "Are differences in sexual preference dictated solely by psychosocial factors, or does biology play a determining role?" LeVay[1] has examined the brains of heterosexual and homosexual males to determine whether there might be neuroanatomic differences that are related to sexual preference. Such a difference was found in the interstitial nuclei of the anterior hypothalamus (INAH-3) cell group.

Allen et al[2] have shown that the volume of the cell group called INAH-3, which participates in the regulation of male-typical sexual behavior in nonhuman primates, is more than twice as large in males as in females. LeVay postulated that the brains of members of either sex who are attracted to females might differ from the brains of those who are attracted to males. Examining the anterior hypothalamus in 41 middle-aged individuals (16 presumed heterosexual males, 19 homosexual males, and 6 heterosexual females), LeVay found that the INAH-3 cell group differed in size between the homosexual and heterosexual males and that the INAH-3 cell group of the homosexual males resembled the structure found in females. This finding suggests that the INAH region is dimorphic with regard to sexual orientation, and may represent a biologic basis for sexual preference and orientation. In this study, LeVay examined the brains of homosexual men but not homosexual women. Previous studies in rats by Rhees et al[3] have shown that size differences in this part of the hypothalamus are influenced by levels of circulating androgens during a sensitive perinatal period; thus, exposure to altered androgen levels during this period may, at least in rats, affect sexual behavior in adult life.

References

1. LeVay S. *Science* 1991;253:1034.
2. Allen LS, et al. *J Neurosci* 1989;9:497.
3. Rhees RW, et al. *Dev Brain Res* 1990;42:17.

Editor's comment: *LeVay's study indicates that structural differences may indeed exist between the brains of heterosexual and homosexual males, a possibility that would move homosexuality further from the outdated definition of a psychiatric "disease" to one of a normal biologic variation. These findings, together with the hormone studies in rats, raise some interesting ethical questions regarding whether attempts might be made to prevent homosexuality in the future by prenatal hormone treatment or other biologic manipulation. Since there have been animal studies indicating that increased prenatal exposure to maternal stress hormones results in a higher frequency of homosexual offspring, it is also interesting to speculate that homosexuality might actually serve as an ecologic contraceptive — overcrowding results in increased maternal stress hormone production, which results in more homosexual offspring, which results in fewer productive unions, etc.*

Finally, these studies are complicated in that some of the subjects (both homosexual and heterosexual) died of AIDS, but certainly the results will trigger additional and much-needed work on this question.

*For further speculation, the reader is referred to an article entitled "Are Gay Men Born That Way?" (*Time *magazine, September 9, 1991).*

Judith G. Hall, MD

Decreased Stature Associated With Moderate Blood Lead Concentrations in Mexican-American Children

The association between blood lead concentration and growth has been difficult to ascertain because the high concentrations of lead are usually found in populations living under poor socioeconomic conditions. This study evaluated the relationship of blood lead concentration to stature and socioeconomic status in a large, representative sample of Mexican-American children.

The Hispanic Health and Nutrition Examination Study (HHANES) was conducted between 1982 and 1984 and characterized the health and nutritional status of 3 geographically distinct Hispanic groups in the United States. Poverty index, stature, hematocrit, hemoglobin, transferrin saturation, and blood lead data were available for 1,454 Mexican-American children. Their ages ranged from 5 to 12 years and their blood lead levels ranged from 0.14 to 1.92 µmol/L. The poverty index ratio (PIR) developed by the National Center for Health Statistics (NCHS) was used to assess socioeconomic status. A PIR >1.0 implies that the family should be able to fulfill its basic necessities. The relationship of blood lead concentration and growth was analyzed through multiple regression analyses. Blood lead concentrations were classified into 2 groups: low lead and high lead, depending on whether blood lead concentration was above or below the age- and gender-specific medians for lead concentration.

The mean blood lead concentrations were 0.51 µmol/L for males and 0.45 µmol/L for females. Age, hematocrit, and blood lead concentrations were the best statistically significant predictors of stature in males and together they accounted for 82% of the variance. For females, age, PIR, and blood lead concentrations were the best predictors and also accounted for 82% of the variance in height. The mean heights of children whose blood lead concentrations were low or high, adjusted for the effects of age and hematocrit in males or age and PIR for females, revealed that children whose blood lead levels were above the median for their age and sex were approximately 1.2 cm shorter than children with blood lead concentrations below the median. The correlation of serum lead with stature was not due to an intercorrelation of serum lead with any of the other variables.

According to the Centers for Disease Control (CDC), lead values <1.20 µmol/L are considered normal. However, this study demonstrated an inverse relationship between stature and blood lead concentrations, although mean blood lead levels were well below 1.20 µmol/L. In addition, this inverse relationship was not due to colinearity of lead and socioeconomic factors as measured by the PIR. The study's finding of an inverse association between stature and blood lead concentration is in agreement with the analysis of the second National Health and Nutrition Examination Survey (NHANES II).

Frisancho AR, Ryan AS. *Am J Clin Nutr* 1991;54:516.
Wapnir RA, et al. *Pediatr Res* 1977;11:153.
Wapnir RA, et al. *Am J Clin Nutr* 1980;33:1071.
Wapnir RA, et al. *Am J Clin Nutr* 1980;33:2303.

Editor's comment: *This well-designed study provides the strongest evidence to date that moderate lead levels, previously considered safe, are associated with reduced stature. The large, representative sample allowed examination of the confounding factors, such as poor socioeconomic status, that plagued other studies. The finding that children of all ages whose lead levels were above the median for age and gender were shorter than children with blood lead concentrations below the median leads to speculation of other effects of chronic lead exposure among this*

population of Mexican-Americans. While the exposure was of sufficient duration to interfere with growth, the more toxic effects of lead and/or other sequelae of lead exposure were not evaluated. Further, the mechanisms by which lead retards growth were not addressed in this study; however, there are indications that nutritional factors may play an important role. In studies of oral lead ingestion in young rats, the intestinal transport capacity for glucose, amino acids, and sodium is altered even before the deleterious effects of lead on the kidney are evident. In addition, dietary inadequacies have been implicated. Epidemiologic studies report an inverse relationship between dietary calcium and serum lead concentrations. Interestingly, because lactase deficiency is more prevalent in Hispanic populations, the correlation of increased blood lead levels and shortened stature may reflect deficiencies in the intake and absorption of dietary calcium in these Mexican-American children. Additionally, elevated blood lead levels are associated with anorexia, either as a primary determinant or secondary to iron deficiency anemia. Progression of weight gain, while not evaluated in this study, would be an important consideration for future studies. Even though the stature reduction associated with these blood lead levels is mild, if it is also associated with compromised nutritional status, then the adverse effects would be of greater concern since the consequences of lead exposure are exacerbated by energy and/or protein restriction.

Although additional research is required to elucidate the nutritional aspects of lead-induced short stature, this paper provides strong support for the reevaluation of the current CDC standards for acceptable blood lead concentration and renewed emphasis should be placed on minimizing the exposure of growing children to lead.

Fima Lifshitz, MD

Standards For Selected Anthropometric Measurements in Prader-Willi Syndrome

Butler and Meaney present anthropometric measurements for children between the ages of 0 to 24 years with the Prader-Willi syndrome (PWS). Seventy-one white subjects who met the clinical criteria for the diagnosis of PWS (infantile hypotonia, hypogonadism, delayed psychomotor development and/or mental deficiency, early-childhood obesity, small hands and feet, and short stature) were included. High-resolution chromosomal analysis demonstrated that 52% of these individuals had an apparent deletion of the proximal long arm of chromosome 15. Anthropometric measurements included weight, length, sitting height, head circumference, head breadth, head length, total hand length, middle finger length, palm length, hand breadth, total foot length, foot breadth, triceps skin-fold thickness, and subcapsular skin-fold thickness. Children below 2 years of age had length measured in the supine position; measurements after this age were made with a balance beam scale and anthropometer. Longitudinal data on several individuals were collected for up to 6 years. Subjects were grouped at either 3- or 4-year age intervals (eg, 0 to 4 years, 4 to 8 years, 8 to 12 years, 12 to 16 years, 16 to 20 years, and 20 to 24 years) and criteria of a sample size of 5 or more subjects per age group were utilized.

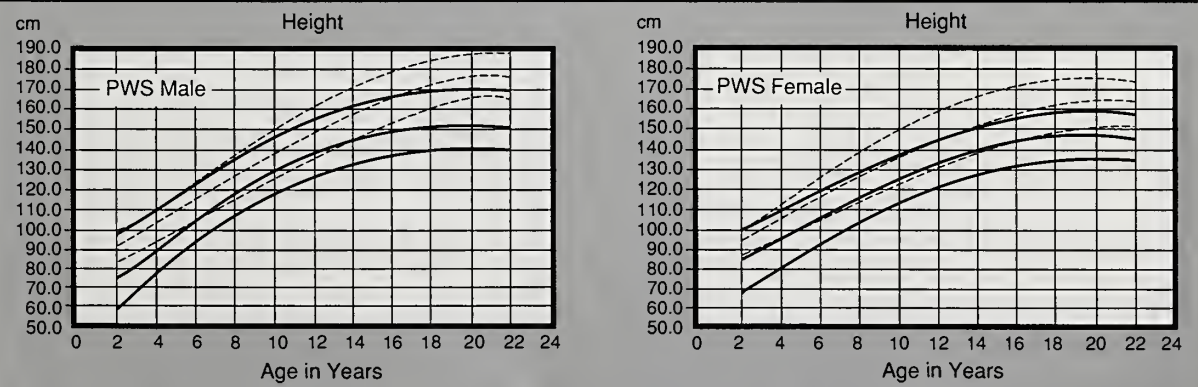
The results for height of males and females are presented in the figure. Sitting height was decreased proportionate to total height. 50th percentile head circumference and head length for PWS males and females during childhood were on approximately the 25th percentile for normal male children until approximately 20-22 years of age when the final measurements fell on the 5th percentile for normal males. Of all measurements taken, only those of the skin folds (triceps and subcapsular) were greater than the data reported for normals. The 50th percentile for skin folds in PWS approximates the 95th percentile of normal females and is above the 95th percentile of normal males and reflects the obesity characteristic of these patients.

Butler MG, Meaney FJ. *Pediatr* 1991;88:853.

Editor's comment: *This is a very detailed anthropometric study of 14 variables in a group of children who are seen frequently in pediatric endocrinology and/or genetics clinics. The incidence of PWS is estimated to be 1 in 16,000 live births, and it is a common form of dysmorphic obesity. The growth curves for height, weight, and other parameters that have been produced for all these variables (see original text) should be useful to clinicians interested in evaluating growth in individuals with this syndrome.*

William L. Clarke, MD

Figure 1
Standardized Curves for Height of Prader-Willi Syndrome



Standardized curves for height of Prader-Willi syndrome (PWS) male and female patients (solid line) and healthy individuals (broken line).
Reproduced by permission of *Pediatr* 1991;88:853.

Effects of Therapy in X-Linked Hypophosphatemic Rickets

Verge et al prospectively studied 24 children (ages 1 to 16 years) with X-linked hypophosphatemic rickets who were treated from 0.3 to 11.8 years with daily calcitriol (25.6 ± 16.9 ng/kg/d) and oral phosphate (100 ± 34 mg/kg/d) administered in divided doses every 4 hours. Patients were evaluated every 3 months for serum electrolytes, blood urea nitrogen, creatinine, calcium, phosphate, and alkaline phosphatase and for height. Calcium, phosphorus, and creatinine were measured in 24-hour urine samples and in random urine samples collected to determine calcium to creatinine ratios. Glomerular filtration rates were measured in 20 patients. Annual height measurements were converted into height standard deviation scores (SDSs) according to data from the US National Center for Health Statistics. To exclude the effects of variation of the onset of puberty and the difficulty of measuring small infants, the first measurements reported were after the age of 2 years and the last were taken before the age of 10 years in girls and 12 years in boys. The mean interval of study of these 13 patients was 5.0 ± 2.3 years.

Growth data were compared to those of 16 untreated prepubertal Australian patients with X-linked hypophosphatemia whose height SDSs were previously reported. Height SDSs also were computed according to the standards of Tanner. Renal ultrasonography was performed every 6 to 12 months. Duration of therapy, age at which therapy was begun, mean and total doses of vitamin D and phosphate, mean serum calcium, number of episodes of hypercalcemia, mean and maximum levels of urinary calcium and phosphorus excretion, number of episodes of hypercalciuria and the mean and maximal products of urinary calcium and phosphorus concentrations were examined as potential risk factors for nephrocalcinosis.

Patients treated with combined calcitriol and oral phosphate for at least 2 years had a mean height SDS (method of Tanner) of -1.08 as compared with -2.05 for the untreated control group (P=0.01). However, the mean change in height SDS of the 13 patients treated for at least 2 years changed only from -1.42 to -1.25 (P=0.05). When the change in the height SDSs were analyzed only with regard to the period of calcitriol and phosphate therapy, mean height SDSs increased from -1.58 to -1.25 (P=0.05). No significant correlation was found between the change in the height SDSs and the duration of treatment or the age at which it began. Nineteen of 24 patients (79%) demonstrated nephrocalcinosis on renal ultrasonography. Regression analysis demonstrated a significant association between nephrocalcinosis and mean daily phosphate dose (r=0.60, P=0.002). Mean serum calcium concentrations in the 24 patients ranged between 2.15 to 2.53 mMol/L (8.6 to 10.1 mg/dL). Fifteen patients had serum calcium concentrations of more than 2.5 mMol/L (10.0 mg/dL) on 1 or more occasions. Eight of the 19 for whom urinary measurements were available had 1 or more episodes of hypercalciuria. These received significantly more calcitriol than those who never had hypercalciuria (29.9 vs 17.3 ng/kg/d, P=0.007); 4 of 20 had a decrease in glomerular filtration rate.

The authors conclude that since X-linked hypophosphatemic rickets is a benign disease compatible with a normal life span, the potentially serious side effect of nephrocalcinosis requires that the treatment regimen be reevaluated. Since the advent of combination therapy with calcitriol and phosphate, few patients now require surgical osteotomy; however, their data demonstrate only a modest effect on final height. They further suggest that since the growth pattern of untreated patients has not been well documented, a prospective controlled trial of combination therapy needs to be undertaken to evaluate its effect on linear growth. The authors recommend the conservative use of phosphate and calcitriol during therapy and regular monitoring for both nephrocalcinosis and periodic determination of glomerular filtration rates.

Verge CF, et al. *N Engl J Med* 1991;325:1843.

Editor's comment: *This very important and interesting article contributes significantly to the information concerning the effects of calcitriol and phosphate in X-linked hypophosphatemic rickets. The authors are correctly concerned with the high frequency of nephrocalcinosis in their patients.*

*An accompanying editorial (*N Engl J Med *1991;325:1875) by Glorieux reviews the classification and therapy of all forms of rickets. Glorieux notes that data developed by Verge et al confirm earlier reports suggesting that phosphate and calcitriol improve the growth rate of children with X-linked hypophosphatemic rickets. However, at least one retrospective study (Stickler GB et al.* Lancet *1989;2:902) concluded that failure of treatment to promote growth and the risks of renal failure suggested that it might be better not to treat these patients at all. Glorieux does not agree with Verge et al that a randomized, placebo-controlled trial should be undertaken. He points to the central role of hypophosphatemia in retarding growth as demonstrated by Harrison et al in 1966 (*Am J Dis Child *1966;112;290-297). In that report, a girl with dwarfism and X-linked hypophosphatemic rickets had severe vitamin D intoxication that permanently reduced her glomerular filtration rate; her serum phosphate had increased to a normal level. Surprisingly, her final adult height reached the 50th percentile. Glorieux concludes that the frequent assessment of renal function is important in caring for these individuals.*

Rickets and growth was recently reviewed in GGH *(7;4:1-3). In that review it was suggested that if treatment starts before the age of 5 years, catch-up growth can be achieved. Readers need to realize that not all investigators agree on the extent of treatment benefit, but all agree that close observation is needed.*

William L. Clarke, MD

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Growth Hormone Resistance and Inhibition of Somatomedin Activity by Excess of Insulin-Like Growth Factor–Binding Protein (IGFBP) in Uraemia

Blum et al measured somatomedin bioactivity (SmBA), insulin-like growth factor 1 (IGF-1) and IGF-2 by radioimmunoassay (RIA); IGF-binding protein 1 (IGFBP-1) and IGFBP-3 by RIA; and free somatomedin-binding capacity (SmBC) in 2 groups of children. Group 1 consisted of 31 children with a mean age of 10.5 ± 4.8 years who had end-stage renal failure (ESRF) and were on dialysis. Group 2, 11 children with a mean age of 7.3 ± 3.1 years, had chronic renal failure (CRF) but with some residual glomerular filtration. All blood samples were taken in the morning.

SmBA, as determined by a porcine cartilage assay, was subnormal in all subjects, while IGF-1 was in the low normal ranges, and IGF-2 was slightly elevated or normal (Figure 1). IGFBP-3 was markedly elevated in those with ESRF and was at the upper range of normal in group 2. In normals, a linear correlation has been found between the sum of IGF-1 and IGF-2 vs IGFBP-3 (r = 0.91) and an exponential correlation has been reported between IGF-1 and IGFBP-3. In renal failure there is a marked deviation from these correlations, with higher IGFBP-3 levels for both IGF-1 plus IGF-2 vs IGFBP-3 and IGF-1 vs IGFBP-3. SmBC was increased in both groups, suggesting that the IGFBP was biologically active. IGFBP-3 of a molecular weight ranging from 12 kd to 150 kd is present in normal serum. However, IGFBP-3–like material in sera from ESRF subjects eluted in the range of 20 kd to 60 kd.

The authors demonstrated that SmBA is significantly decreased in patients with ESRF while serum IGF-1 and IGF-2 levels are in the normal range, and that IGFBP-1 and IGFBP-3 are elevated. They concluded that the excess of IGFBP-3 related peptide rather than IGFBP-1 plays a role in the inhibition of IGF activity. Indeed, the molar ratio of total IGF and IGFBP-3 is approximately 1.0 in normals but a large excess of IGFBP-1–like and IGFBP-3–like materials are present in uremia, suggesting a relative deficiency of IGF in these individuals. Since free SmBC was increased in the patients with CRF, the authors suggest that the excess of IGFBP is, in fact, biologically active. The authors further suggest that when renal function is impaired, low-molecular-weight IGFBPs accumulate, leading to an excess of IGFBP. This excess IGFBP results in a "sequestration" of IGF and an inhibition of IGF activity. Thus, IGFBP in uremia acts as a somatomedin inhibitor. The authors also conclude that IGF production itself is decreased in uremia, possibly as a result of an impaired growth hormone post-receptor event.

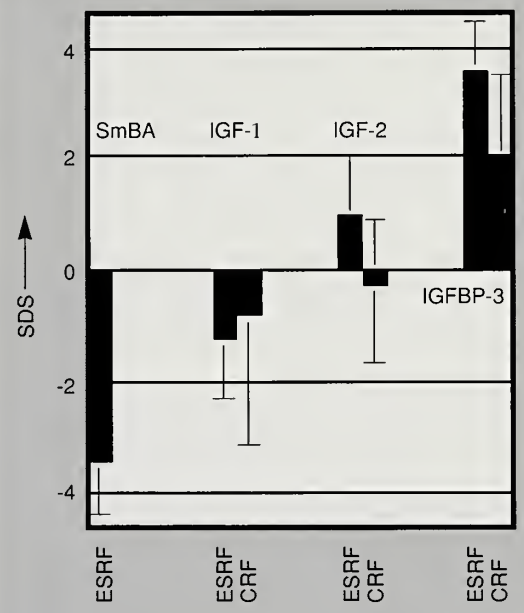
The following hypothetical schematic model is proposed. IGF-1, IGF-2, and IGFBP are produced in the liver and free IGF-1 and IGF-2 bind to IGFBP-3, which binds to a nonbinding subunit to form a high-molecular-weight complex, which remains in the circulation. While in equilibrium in normals, IGFs are released to act on their target cells, and low-molecular-weight IGFBP forms are cleared by the kidney. In renal failure, this clearance is impaired, and the IGFBPs accumulate in the circulation, leading to an excess of IGFBP over IGF. Thus, free biologically available IGF is lowered. In addition, IGF secretion is low.

Blum WF, et al. *Pediatr Nephrol* 1991;5:539.

Editor's comment: *This is an elegant paper that demonstrates important findings concerning circulating growth factors and their binding proteins in uremic children. The findings suggest a possible mechanism for growth failure in uremic children whose growth hormone secretion may be within normal limits. It also suggests reasons why these children may respond favorably to the administration of exogenous growth hormone with an improvement in height velocity. The paper would have been more interesting had the authors included more information concerning the children who were studied. Of particular interest would have been information concerning growth velocity and growth hormone secretion at the time of the study. Combined with previously reported data on GH failure in CRF (Schaefer et al,* GGH *1991;7:2), and GH pulsatility and linear growth response to exogenous GH (Rees et al,* GGH *1991;7:2), the data concerning the pathophysiology of growth in CRF is becoming more understandable.*

William L. Clarke, MD

Figure 1



Serum somatomedin bioactivity (SmBA), insulin-like growth factor 1 (IGF-1), IGF-2 and IFG-binding protein-3 (IGFBP-3) in patients with end-stage renal failure (ESRF) and chronic renal failure (CRF) with residual renal function. Except for SmBA (n=11) the number of patients in each group was 31 for ESRF and 11 for CRF. Values are given as standard deviation scores (SDS) because of their age dependence.

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July 12-15, 1992 24th Ann March of Dimes Clinical Genetics Conf, Stanford, CA. Info: Prof Svs Dept, March of Dimes Birth Defects Found. Tel: 914-428-7100.

July 20-31, 1992 Bar Harbor Mammalian Genetics Course, Bar Harbor, ME. Info: J Musetti. Tel: 207-288-3371 ext. 1253.

August 5-9, 1992 The David W Smith Workshop (Malformation and Morphogenesis), Wake Forest Univ, Winston-Salem, NC. Info: J Dean. Tel: 803-223-9411, Fax: 803-227-1614.

August 30 - September 5, 1992 9th Int'l Congress of Endo, Nice, France. Info: NICE 92, c/o SOCF1, 14 Rue Mandar, 75002 Paris, France.

September 7-10, 1992 31st Ann Mtg of the ESPE, Zaragoza, Spain. Info: Dr A Ferrandez-Longas, Endocrine Unit, Miguel Servet Children's Hosp, Paseo Isabel la Catolica 3, 50009 Zaragoza, Spain. Tel: 34-76-355700.

September 10-12, 1992 Int'l Congress on Growth Hormone and Somatomedins During Lifespan, Milan, Italy. Info: Drs D Cocchi/V Locatelli, Dept of Pharm, Univ of Milan Sch of Med, Via Vanvitelli, 32, 20129, Italy.

October 8-9, 1992 Int'l Symp on Growth '92 - 2 Decades of Experience in Growth, Santiago de Compostela, Spain. Info: Dr S Rossetti, Ares-Serono Symposia, Via Ravenna 8-00161 Rome, Italy. Fax: 39-6-44291324.

October 10-14, 1992 44th Postgrd Assembly of the Endo Soc, Boston, MA. Info: A Singer, The Endo Soc. Fax: 301-571-1869.

November 4-7, 1992 The Role of Insulin-like Growth Factors in the Nervous System, Arlington, VA. Info: The New York Academy of Sciences. Tel: 212-838-0230; Fax: 212-888-2894.

November 9-13, 1992 Ann Mtg of Am Soc of Human Genetics, San Francisco, CA. Info: M Ryan, ASHG. Tel: 301-571-1825; Fax: 301-530-7079.

December 3-6, 1992 Growth Hormone II: Basic and Clinical Aspects, Tarpon Springs, FL. Chairpersons: Drs B Bercu/R Walker. Info: Serono Symposia, Dr B Burnett. Tel: 617-982-9000; Fax: 617-982-9481.

June 3-7, 1993 4th Joint Mtg of the LWPES/ESPE, San Francisco, CA. Info: Prof M Grumbach, Univ of CA Sch Med. Tel: 415-476-2244; Fax: 415-476-4009.

June 9-12, 1993 75th Ann Mtg of the Endo Soc, Las Vegas, NV. Info: A Singer, The Endo Soc. Fax: 301-571-1869.

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Current Status of Somatic Gene Therapy

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Genetic therapy for human disease has been variously heralded as a panacea or as a threat to fundamental human and ethical values.[1-3] Since the initiation of clinical trials involving gene transfer[4] and gene therapy[5] at the National Institutes of Health (NIH) in 1989, the hyperbole that has often surrounded this debate has ceded to a more critical assessment of the clinical indications for gene therapy for specific disease processes. While the therapeutic efficacy of somatic gene therapy has not yet been established for any specific disease in either animal models or clinical trials, experimental data demonstrate that the safety of somatic gene transfer is commensurate with that of conventional experimental therapeutic agents. Various regulatory bodies, including the Recombinant DNA Advisory Committee and the Food and Drug Administration, have demonstrated their willingness to approve judicious clinical trials aimed at establishing the feasibility and safety of somatic gene transfer procedures. The number of clinical trials involving gene transfer and gene therapy is increasing at a rapid rate, and it is likely that the first commercial products will be in Phase II or Phase III trials and licensed within several years. This review describes current methods that may be employed for somatic gene therapy with particular reference to those that may be applicable to endocrine disorders and disorders of growth.

PRINCIPLES AND APPROACHES TO SOMATIC GENE TRANSFER

The basic principle of somatic gene therapy is that recombinant genes can be introduced into somatic cells to alter the course of a disease process. Most research has focused on single-gene disorders based on the paradigm that inherited defects in essential genes might be treated by introducing a normal copy of that gene into somatic cells. While single gene disorders represent models for basic research, these disorders are rare. If somatic gene therapy is to have a significant impact on medical practice, it will be for polygenic, multifactorial, and acquired diseases, which are more common.

The initial clinical trials of somatic gene therapy at the NIH provide examples for gene therapy of both monogenic and polygenic disorders. The clinical trial of gene therapy for adenosine deaminase deficiency[5] involves introducing a normal copy of this gene into genetically deficient T cells to correct severe combined immunodeficiency disease (SCID).

In This Issue

Another clinical trial involves treating solid tumors by introducing a gene for tumor necrosis factor into a select population of T cells (tumor-infiltrating lymphocytes) that are capable of migrating to the tumor and delivering a high level of this natural antitumor agent specifically to these sites.[6]

Somatic gene therapy as currently conceived does not involve the repair or removal of genes bearing pathogenic mutations; most importantly, it does not involve any manipulations of the inherited germ line. While technologies for site-specific modification (homologous recombination) of genes in embryonic cells are well developed in mice, these techniques have not yet been applied successfully in other species. These technologies also raise difficult ethical and social issues, and it is unclear when such interventions would be clinically indicated.

METHODS FOR SOMATIC GENE TRANSFER

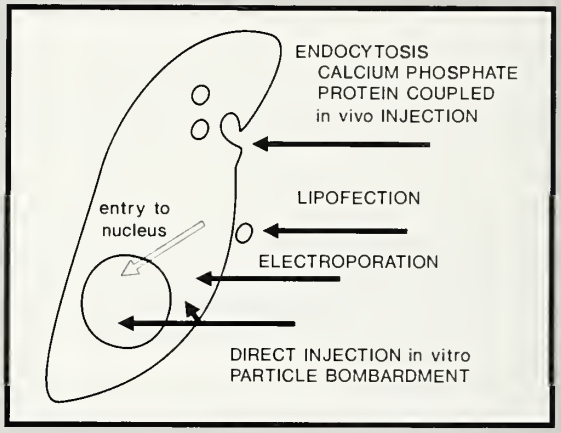
The enabling technology for somatic gene therapy is the ability to transfer recombinant genes into somatic cells. Two major methods can be distinguished: *DNA-mediated gene transfer* involves introducing pure DNA or complexes of DNA bound to various carriers into cells and is referred to as *transfection*. *Viral-mediated gene transfer* involves the use of viral particles as vehicles for delivering genes to cells by the process of infection and is commonly referred to as *transduction*.

DNA-Mediated Gene Transfer

DNA-mediated gene transfer is based on the observation that cells in culture that are exposed to DNA in various forms can take up these molecules and express the gene products that they encode. The classic methods for transduction is *microinjection*, in which DNA is physically injected into the nucleus of cells in culture.[7] Other methods include administration of calcium phosphate precipitates,[8] *electroporation*,[9] *lipofection/liposome fusion*,[10] particle bombardment with DNA bound to magnetic particles,[11] and receptor-mediated uptake by DNA protein complexes.[12] The mechanism by which cells take up and express DNA remains unclear, but for several of these methods it is thought to involve endocytosis of DNA into cells and release from endosomes before degradation is complete (Figure 1). Recent data suggest that the admixture of DNA with adenoviral particles, which enhance the release of endosomal contents into the cytoplasm, can increase the efficiency of some methods of transfection more than a thousandfold.[13]

When DNA is taken up by cultured cells, recombinant gene expression is detected for a short period; this is referred to as a period of *transient expression*. *Stable* integration of DNA into the chromosomes of transfected cells is rare.

Figure 1
Mechanisms of DNA-Mediated Gene Transfer



Schematic of DNA uptake into cells by DNA-mediated gene transfer. Exposure of cells to DNA, DNA precipitated with CaPO4, or DNA coupled to trophic peptides results in uptake by cells by endocytosis. Exposure of cells to DNA packaged in liposomes leads to uptake by membrane fusion. Exposure of cells to DNA in the presence of a strong electric pulse results in the creation of pores in the membrane and electrophoresis of DNA into the cell. DNA also can be introduced directly into the cell or nucleus by injection or bombardment with DNA-bound magnetic particles. The mechanism by which DNA enters the nucleus remains unknown.

The possibility of DNA-mediated gene transfer in vivo was suggested by early experiments in which the injection of viral DNA into animals resulted in the production of infectious virus particles. Recent research demonstrates that injection of DNA into muscle[14] and thyroid[15] leads to uptake and expression of recombinant sequences into these cells in vivo. DNA-mediated gene transfer into hepatocytes has been achieved by injecting DNA/asialoglycoprotein complexes, which are specifically taken up into the liver via the asialoglycoprotein receptor.[12] In the liver and thyroid, transient expression of injected genes is observed for several days. In muscle, more prolonged, although not permanent, expression has been observed.[14]

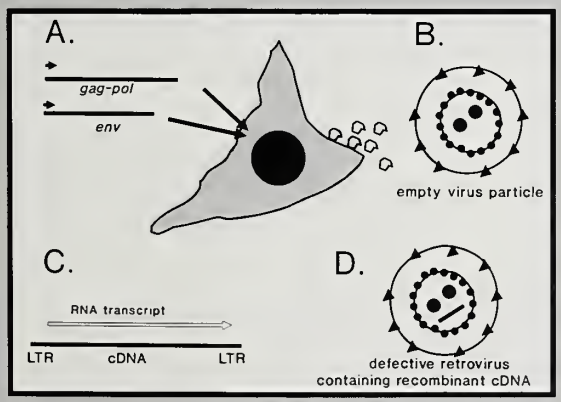
Viral-Mediated Gene Transfer

The principle of viral-mediated gene transfer, or transduction, is that viral vectors could be used as a "Trojan horse" for introducing recombinant gene sequences into cells. Since viral infection is highly efficient, and since some viruses stably integrate their genome into the chromosomes of the infected cells, viral-mediated gene transfer has been viewed as the preferred method for attaining efficient long-term expression of recombinant genes.

Viral vectors based on the Moloney murine leukemia virus[16] have been employed in each of the clinical trials performed to date and are presently the vectors of choice for somatic gene therapy. The use of retroviral vectors for gene therapy is based on the fact that it is possible to separate the process of producing a viral particle from the process of packaging a recombinant gene into these particles (Figure 2).

A cell that is genetically modified to express the viral proteins *gag-pol* and *env* in the absence of an intact viral genome will assemble viral particles and is referred to as a *packaging cell line*. If another gene is introduced into these cells, which contains a human cDNA along with the ψ (packaging) sequence and dual *long terminal repeat* (LTR) sequences, the transcript bearing the ψ sequence will be packaged into the empty viral particles. This produces a *defective retrovirus*, which is capable of infecting target cells and permanently introducing the recombinant gene into the chromosome but which does not contain genes encoding any viral proteins and is incapable of expressing any viral functions.

Figure 2
Mechanisms for Synthesizing Defective Retroviral Vector



Schematic of strategy for producing defective retroviral vectors for viral mediated gene transfer. If a cell is transfected with genes encoding the 3 major retroviral proteins *gag-pol,* and *env* (A), these gene products will self assemble and bud off empty virus particles (B). If an expression vector containing the packaging signal (ψ) and LTR sequences is introduced into this cell, the RNA transcript from this vector will be packaged into the empty viral particles, producing a defective retrovirus capable of being used for gene transfer (D).

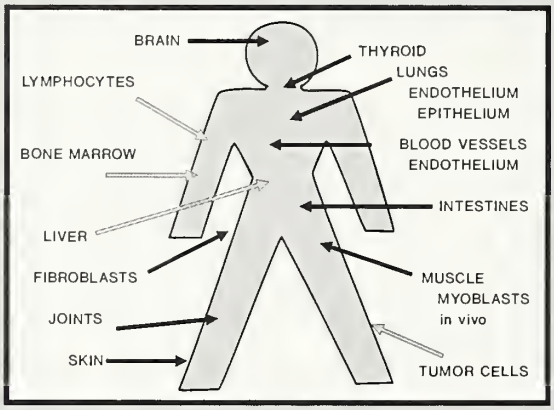
Extensive safety testing in nonhuman primates,[17] the results of initial clinical trials,[4] and the fact that there is no known pathology caused by similar viruses that are ubiquitous in our environment suggest that these agents are relatively safe. There continues to be concern about the theoretical risk of malignancies due to insertional mutagenesis and the potential for homologous recombination with wild-type viruses, but these risks are calculably small.[18]

Retroviral vectors have been shown to be capable of transducing a variety of cell types that could be targets for gene therapy, including hematopoietic progenitors, lymphocytes, hepatocytes, fibroblasts, endothelial cells, keratinocytes, thyroid follicular cells, and others. One of the limitations of retroviral vectors is that stable gene transfer requires cell division, thus restricting the potential targets for these vectors. Recently, adenovirus[19] and adeno-associated virus[20] have been proposed as vehicles for somatic gene therapy. These vectors may have advantages for certain clinical applications, although there are presently less data on feasibility and safety than there are for retroviral vectors.

SOMATIC TARGETS FOR GENE THERAPY

Many somatic targets may be considered candidates for somatic gene therapy (Figure 3, page 4). The major focus of gene therapy research has been to develop methods for introducing recombinant genes into different somatic sites and achieving stable and appropriately regulated expression of recombinant genes. Each target tissue presents different problems of molecular biology, gene regulation, cell biology, and surgery, which will not be reviewed in detail here. Three somatic targets are currently the object of clinical trials. Bone marrow was initially considered an ideal candidate for somatic gene therapy since transduction of a discrete population of stem cells would theoretically replenish the entire mass of marrow-derived elements. Progress has been inhibited by the complexity of recognizing the pluripotential stem cell and attaining appropriate expression of recombinant genes through the process of differentiation. The first clinical trials of somatic gene transfer involved introducing genes

Figure 3
Targets for Somatic Gene Therapy



Potential targets for somatic gene therapy. Many cells and organs have been considered targets for gene therapy in in vitro or animal experiments. Those targets indicated by shaded lines are currently under clinical investigation.

into T cells collected from tumors (tumor-infiltrating lymphocytes) or peripheral blood (peripheral blood lymphocytes).[4-6] The limited life span of these cells after transplantation limits the scope of this approach to gene therapy. Hepatocytes represent another target for clinical trials of somatic gene therapy.[21-23] The demonstration that hypercholesterolemia in the low-density lipoprotein (LDL) receptor—deficient Watanabe rabbit could be ameliorated by introducing a recombinant LDL-receptor gene into hepatocytes represents the first successful application of somatic gene transfer to alter a systemic phenotype in animals.[24] This approach to somatic gene therapy is limited by the difficulty of large-scale hepatocyte cultivation and the lack of clinical precedent for hepatocellular transplantation.

DNA-mediated gene transfer into the liver,[11] muscle,[13] and thyroid[14] has been demonstrated in animal models. This method is generally simpler than viral-mediated gene transfer, although it generally results in only transient expression of the gene product. There is considerable interest in using gene transfer into muscle to treat muscular dystrophy, produce hormones or enzymes, or provide vaccines.

APPLICATIONS OF SOMATIC GENE THERAPY IN GROWTH AND DEVELOPMENT

In considering somatic gene therapy for a specific disease, it is necessary to have a clear understanding of the molecular nature of the disease process, how a discrete molecular intervention would alter the course of the disease,[25] and how the potential benefits balance the risks of this highly experimental therapy.[26] Inborn errors of metabolism are frequently associated with poor growth and impaired development and are considered important models for somatic gene therapy.[25] Inherited disorders of endocrine factors such as growth hormone, parathyroid hormone, or thyroid hormones also are attractive candidates for somatic gene therapy, and progress has been made in developing a gene therapy for each of these disorders. Somatic gene therapy not only is applicable to rare inherited defects in single genes but also can be used to alter the course of polygenic or multifactorial processes too numerous to list. Gene transfer could be used to provide hormones that are deficient because of acquired diseases such as diabetes mellitus (type I) as well as increasing expression of hormones such as growth hormone to alter complex disease states or even aging. Recent reports demonstrate that significant systemic levels of growth hormone can be achieved in vivo by gene transfer into muscle cells using either viral or DNA vectors.[27-28]

The critical element in using gene transfer methods to supply essential endocrine factors is to achieve proper regulation of the recombinant gene product. This can be achieved by constructing vectors with regulated promotor elements, by the choice of target tissue that responds to different endocrine or paracrine factors, and by considering different modes of gene delivery (stable versus transient).

In considering somatic gene therapy for genetic diseases affecting growth and development, one rapidly confronts the specter of using the same technologies to enhance normal growth. While somatic gene transfer as a means for treating human disease has come to be almost universally accepted by ethicists, theologians, and legal bodies,[22] the notion of enhancement engineering continues to be viewed with concern. There is no way to ensure that genetic technologies will not be abused by individuals seeking personal enhancement. What is critical is to ensure that gene therapy is seen only as a means for allopathic correction of recognized diseases and that any application of gene therapy meets the highest possible standards of safety, fairness, and voluntary informed consent. With these cautions, it is likely that somatic gene therapy will be widely studied in the coming decade as a means for treating a wide variety of genetic and acquired diseases, and that this technology may have a significant impact on the practice of medicine.

ACKNOWLEDGMENTS

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Letter From the Editor:

Dr. Herbert Miller, a highly respected senior pediatrician with a longtime interest in neonatology, submitted the following paper as a follow-up to that published by Dr. Joseph Warshaw in *GGH* Vol. 8, No. 1. It will be of interest to those who work with small or intrauterine growth restricted infants.

Robert M. Blizzard, MD

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Intrauterine Growth Retardation: Past, Present, and Future

Herbert C. Miller, MD
Professor Emeritus of Pediatrics
University of Kansas Medical Center

The summary of a recent review[1] of fetal growth retardation makes the strong statement that epidemiologic research of intrauterine growth retardation (IUGR) continues to be "hampered by the lack of a broadly used standard for defining fetal growth." The need for such a standard is long overdue, but the problems associated with all aspects of IUGR in the United States go beyond just the need for a "broadly used standard." Investigators do not agree on whether there are different types of IUGR or if IUGR is an entity to be diagnosed solely by a low birth weight for gestational age; the causes and prevalence of IUGR differ widely among investigators.

Many of the faults associated with IUGR in the United States are illustrated in a recent meta-analysis[2] of 6 published studies that suggested the occurrence of IUGR among infants born to mothers with pregnancy-induced hypertension was reduced by 44% among mothers taking daily doses of aspirin in amounts of 50 to 150 mg during the second and third trimesters. The diagnosis of IUGR in the meta-analysis was made on the basis of a birth weight below the 10th percentile for the infant's gestational age. No mention was made of which of the several standards was used in diagnosing IUGR, which of the several types of IUGR was reduced in frequency by prophylactic aspirin, whether the mothers had additional risk factors in their pregnancies, whether the women were white or black, or whether the infants were preterm or full term.

In his review of IUGR, Warshaw[1] recognized 2 types of IUGR: the symmetric and the asymmetric. In the symmetric type, he indicated that body weight, crown-heel length, and head circumference showed the same degree of growth restriction at birth, and stated that most infants with this pattern born after 36 weeks gestation continued to exhibit sluggish postnatal growth. It is not clear whether the reduction in body weight was solely dependent on the reductions in crown-heel length and head circumference or also involved a reduction in soft tissue mass. Some newborn infants have small skeletal dimensions for their gestational ages, including short crown-heel lengths and small head circumferences, that occur in combination with significant reductions in soft tissue mass. These infants with the combined pattern of reductions in skeletal size and soft tissue mass have the most severe type of IUGR, a condition that occurs less frequently than infants with the asymmetric type.[3] Warshaw does not describe which parameters of growth are retarded in the asymmetric type.

As described by Gruenwald[4] nearly 30 years ago, asymmetric infants at birth can have significant reductions in soft tissue mass with normal lengths for their gestational ages, or they can have significant reductions in crown-heel lengths for their gestational ages without reductions in soft tissue mass.[4] Warshaw does describe distinct differences in postnatal growth in infants with the asymmetric type of IUGR resulting from nutritional compromise; one group showed rapid catch-up growth after birth, but approximately one third of the asymmetric infants were still below the 5th percentile at 2 years of age. The differences in postnatal growth suggest that the infants who had rapid catch-up growth also had reductions in soft tissue mass and normal crown-heel length, and infants with sluggish growth in the first 2 postnatal years had short crown-heel lengths for their gestational ages and normal amounts of soft tissue, especially subcutaneous fat. These conclusions are based on follow-up studies of infants born at the University of Kansas Medical Center with these 2 different types of asymmetric fetal growth.[5]

Diagnosing IUGR by types increases the reported frequency of IUGR substantially, compared with diagnosing IUGR solely by low birth weight for gestational age.[6]

Warshaw's recent review of IUGR suggested that the standards developed by Brenner and colleagues[7] might serve as an example for evaluating fetal growth in newborn infants. Their standard was based on infants born during the period from 1962 to 1969 and was limited to birth weights of infants with gestational ages of 21 to 44 weeks.[7] Corrections were made for parity, race, and sex, with gestational ages ranging from 36 to 42 weeks inclusively. No standard was provided for evaluating whether infants had abnormally short crown-heel lengths or had normal body lengths at birth. No standards were provided for evaluating head circumferences at birth.

It is important to recognize that the types of IUGR that occur at birth also occur in older infants and young children and are diagnosed by careful measurements of height and weight. There are no valid reasons for not making careful measurements of crown-heel lengths, head circumferences, and weights at birth. The types of IUGR that occur in newborn infants can be suspected by simple inspection of the infants; however, for the sake of the infant, parents, and other physicians caring for newborn infants, it is important to carefully make and document measurements.

The problems associated with the diagnosis of IUGR in the United States are so manifold and so important that a national committee of obstetricians and pediatricians should be given the task of trying to establish guidelines for diagnosing IUGR in newborn infants, including standards of fetal growth.

In Future Issues:

Fragile X Syndrome: Review and Current Status
by David L. Nelson, PhD

Effects of Drugs and Other Chemicals on Fetal Growth
by J.M. Friedman, MD, PhD

Relevance of Developmental Genetics to Human Malformations
by Golder N. Wilson, MD, PhD

Sleep, Growth Hormone Secretion, and Short Stature
by Richard H. Wu, MD, and Paul Saenger, MD

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The Effects of Irradiation on Endocrine Function in Children

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Radiation may directly impair hypothalamic, pituitary, thyroid, and gonadal function or, alternatively, induce the development of hyperparathyroidism, thyroid adenomas, or carcinomas. Clinical presentations include short stature, failure to undergo normal pubertal development, precocious puberty, hypothyroidism, thyroid tumors, gynecomastia, infertility, and varying degrees of hypopituitarism.

GROWTH IMPAIRMENT

A number of factors may adversely affect growth in children with tumors, including radiation damage to the hypothalamic-pituitary axis (HPA), a direct radiation effect on growing bones, hypothyroidism and precocious puberty secondary to irradiation, cytotoxic chemotherapy, malnutrition, residual tumor, corticosteroid therapy, and graft-versus-host disease in those receiving bone marrow transplantation.

Hypothalamic-Pituitary-Adrenal Axis

Deficiency of one or more anterior pituitary hormones is a recognized sequel of external radiotherapy to the HPA in childhood. The radiotherapy may be part of the treatment for a brain tumor distant from the HPA or for acute lymphoblastic leukemia (ALL), retinoblastomas, or nasopharyngeal tumors. With radiation of the HPA, growth hormone (GH) is always the first hormone to be affected. Gonadotropin (Gn), corticotropin (ACTH), and thyrotropin (TSH) deficiencies usually follow in that order. Littley et al[1] reported that 5 years following 3.75 to 42.5 Gy, all patients treated were growth hormone deficient (GHD), 91% Gn, 77% ACTH, and 42% TSH deficient. The degree of hormonal deficit is related to the radiation dose. Following lower radiation doses, isolated GHD occurs, while higher doses may result in panhypopituitarism. The speed of onset of GHD also is dose-dependent; the higher the radiation dose, the sooner GHD ensues.

Moell et al[2,3] described reduced spontaneous GH secretion using 24-hour profiles in prepubertal and pubertal girls following cranial irradiation for ALL (20 to 24 Gy). The expected increase in GH secretion at puberty did not occur, and there was attenuated pubertal growth.

The dose of irradiation employed in prophylactic cranial irradiation for ALL recently was reduced to 18 Gy. Results of recently completed studies by Crowne et al[4] of GH secretion after 18 Gy of cranial irradiation in children differed from those obtained by Moell et al.[3] Spontaneous GH secretion was normal in prepubertal children, but pubertal children showed abnormalities of spontaneous GH secretion despite the fact that each underwent puberty spontaneously and showed normal sexual progression. There was both reduced secretion of GH and significant disturbance in the periodicity of GH secretion in these children.[4]

Spinal Irradiation

Brain tumors with potential to disseminate within the central nervous system usually are treated with craniospinal irradiation, and the whole spine is included within the radiation field. The radiation field in the management of other tumors, for example flank irradiation in Wilms' tumor, also includes part of the spine. We demonstrated that whole spine irradiation of 27 to 35 Gy will appreciably impair spinal growth.[5] Our most conservative figures indicate that the eventual loss in height is 9 cm when irradiation is given at 1 year of age, 7 cm when given at 5 years, and 5.5 cm when given at 10 years.

Both standing and sitting height standard deviation scores (SDSs) were more negative for children receiving craniospinal irradiation than for those receiving only cranial irradiation (Figure 1, page 8).

Precocious Puberty

Early puberty occurs in some children receiving cranial irradiation for brain tumors and ALL.[6] Puberty in children with radiation-induced GHD occurs at a significantly earlier chronologic and bone age than in children with spontaneous isolated idiopathic GHD. Both sexes are affected, although the female is more vulnerable to lower radiation doses. Leiper et al[6] reported that the mean age of onset of puberty in 23 girls with early puberty secondary to 18 to 24 Gy of cranial irradiation was 8.8 years, greater than 2 SD from the mean of normal girls. These 23 girls were treated at a mean age of 4 years.

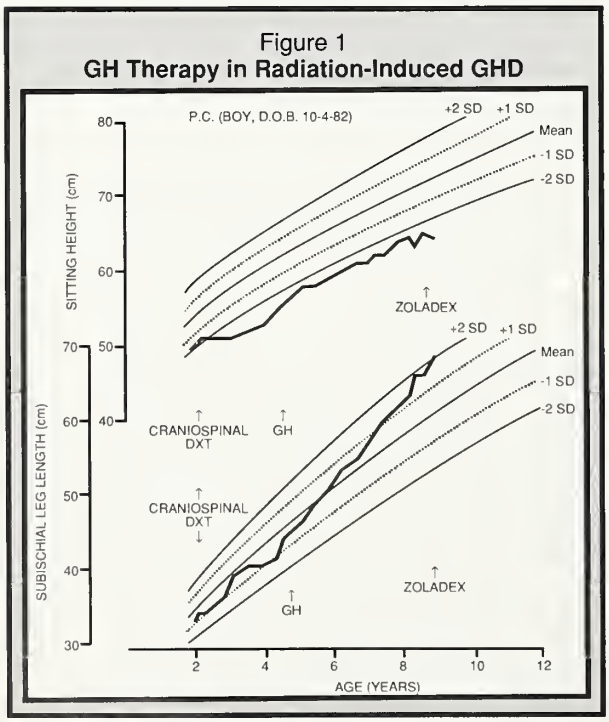
INDICATIONS FOR GROWTH HORMONE THERAPY

Long-term studies following GH therapy are essential. Ideally, these should include an analysis of the final height and gain or loss in stature (SDSs) from initiation of GH therapy until the end of growth in children with radiation-induced GHD and compared with data from similar patients not receiving GH. Shalet et al[7] and Sulmont et al[8] reported that GH therapy was of significant benefit in children with radiation-induced GHD; however, the height gained, or rather the "height loss" that had been prevented, was disappointingly small and much less than that seen in GH-treated children with idiopathic GHD. A number of factors contributed to the suboptimal growth response, including spinal irradiation, early puberty, an extended interval (mean, 6.0 years) between irradiation and the initiation of GH therapy, and the inadequacy of the GH dosage used in the early studies.

The chances of recurrence of a brain tumor are greatest within 2 years of the primary treatment of the tumor. No evidence exists that GH treatment increases recurrence rates of brain tumors in children with radiation-induced GHD. A reasonable approach, therefore, 2 years after treatment is to consider GH therapy for children with brain tumors treated by standard radiation schedules, including a dose to the HPA in excess of 30 Gy. At this time, cytotoxic chemotherapy is completed. The chance of tumor recurrence is low, and it has been established that most patients will be GHD. In some centers, endocrinologists offer GH therapy routinely at 2 years without recourse to GH tests or evidence of impaired growth. In other centers, endocrinologists insist on biochemical evidence of GHD and a subnormal growth rate. In our institution, we establish GHD biochemically and then consider GH therapy independent of the growth rate in GHD patients. These guidelines assume that in craniospinal-irradiated children, growth is assessed by leg length velocity and that other causes of poor growth such as radiation-induced hypothyroidism, recurrent tumor, and malnutrition have been excluded.

In practice, our management attempts to match the timing of the introduction of GH therapy with the special circumstances, age, pubertal status, and needs of the individual. Early treatment is particularly suitable for the craniospinally treated young child of short parents, although disproportionate growth may occur (Figure 1).

Figure 1
GH Therapy in Radiation-Induced GHD



ACUTE LYMPHOCYTIC LEUKEMIA

Much confusion and controversy have been generated over the growth patterns and GH requirements of the child with ALL treated with prophylactic cranial irradiation and combination cytotoxic chemotherapy. Some groups report no adverse effects on final height. Others have noted a modest adverse effect on growth.[7] Since final height is unknown in most of the children reported, the possibility of impaired pubertal growth may mean that final height loss is substantial in a minority of children. Kirk et al[9] reported significant retardation of growth. They reported marked slowing of growth 3.0 to 9.5 years after diagnosis in 77 children treated for ALL with chemotherapy plus 24 Gy of radiotherapy as cranial prophylaxis. The Z score, which reflects the deviation of height measurements from the population mean, was used to assess height change. The mean Z score was +0.16 at diagnosis and -1.37 6 years later. Height for age fell by more than 1 SD in 71% of the survivors after 6 years. Younger children and those tall for age at diagnosis were more severely affected. Thirty of 46 patients tested had partial or complete GHD as determined by provocative testing. Analysis of the radiation schedules and chemotherapy protocols used in different centers has led to some understanding of the explanation for the differences in height loss observed between groups. For example, the duration and nature of the combination cytotoxic chemotherapy may influence the growth prognosis. After treatment

with regimens used in the United Kingdom, the effects of cytotoxic chemotherapy are likely to be minor. More intense cytotoxic chemotherapy regimens have had a profound impact on growth.[9]

For many reasons, the need for treatment with GH is more difficult to predict after treatment for ALL than after a brain tumor. One relates to the dissimilar growth patterns observed by different groups in children with ALL.[10,11] The clinical dilemma is how to identify the few who should receive treatment. In general, we suggest that in the presence of biochemical evidence of GHD, those children who are below the 10th percentile, or those whose growth rate is persistently poor after completion of cytotoxic chemotherapy should be considered for a therapeutic trial of GH.[7] GH therapy is usually warranted in short peripubertal children who received 18 Gy of cranial irradiation.

TOTAL BODY IRRADIATION

Following total body irradiation (TBI), severe growth disturbance is common[12] and may be caused by various etiologic factors, including GHD, thyroid dysfunction, radiation-induced impairment of skeletal growth, or graft-versus-host disease and its treatment. GHD may occur even if the child has not received prophylactic cranial irradiation previously and whether or not the TBI schedule consisted of a single or fractionated dose.

Papadimitriou et al[13] presented preliminary data that suggested a modest benefit followed GH therapy in children with TBI-related growth failure. There was an increase in height velocity adequate to restore a normal growth rate but catch-up growth did not occur. However, the heterogeneous nature of the 13 patients studied confused the issue. Furthermore, the mean age (12.2 years) at which GH therapy was introduced was late.

Graft-versus-host disease and hypothyroidism must be excluded in children who are growing poorly following TBI. Following this, standard provocative tests of GH secretion are required. If the GH responses are subnormal, GH therapy should be offered. If GH responses are normal, a number of questions remain. Is the child growing slowly because of radiation-induced skeletal dysplasia or because of GH neurosecretory dysfunction? Should a 24-hour GH profile be performed to try to establish the latter diagnosis, or should the child receive empiric GH therapy on a trial basis? If GH therapy is instituted, what is the optimum schedule in the possible presence of radiation-induced skeletal dysplasia? As is evident from these questions, there is a desperate need for more information on the impact of single and fractionated courses of 10 to 13 Gy total body irradiation on the incidence of GHD, on the frequency of GH neurosecretory dysfunction, and on the speed of onset of GHD, as well as on the effect of this dose on the natural history of radiation-induced skeletal dysplasia.

THYROID DISEASE

The most important complications of radiation to the thyroid gland are hypothyroidism and thyroid tumors.[14] An association between X-ray exposure and thyroid cancer was suggested by Duffy and Fitzgerald.[15] More recently (1989), Ron et al[14] studied 10,834 children who received X-ray therapy for tinea capitis between 1948 and 1960. These were compared with 10,834 nonirradiated controls and 5,392 nonirradiated siblings. Ninety-eight thyroid tumors (~1:100) were identified among the exposed, and 57 (~1:280) among the nonirradiated. An estimated dose of 0.09 Gy was linked to a fourfold increase of malignant tumors and a twofold increase of benign tumors.

Thyroid Dysfunction

Thyroid dysfunction, after irradiation and cytotoxic chemotherapy in adults with Hodgkin's disease, ranges from frank hypothyroidism with increased TSH and low T_4 concentrations to compensated thyroid dysfunction with raised TSH, but normal T_4 levels.[16] After a radiation dose to the neck of 40 to 50 Gy (fractionated dose) was given to similar patients,[17] approximately 25% of patients showed elevated TSH and low T_4 concentrations, while a further 41% had raised TSH levels in the presence of normal T_4 levels. The time interval between thyroid irradiation and the peak incidence of thyroid dysfunction is unknown. However, the low incidence of thyroid dysfunction (14%) after 1 year rose to a cumulative incidence of 66% 6 years postirradiation.[17]

Children whose thyroid glands are irradiated during craniospinal irradiation for brain tumors, or during TBI before bone marrow transplantation, are vulnerable to thyroid dysfunction. Of significant importance is the finding that the incidence of thyroid dysfunction (16%) following fractionated TBI is much lower than that reported after single fraction TBI (39% to 59%).[12] The incidence may vary with time as recovery of thyroid function has been observed in patients with documented thyroid dysfunction following TBI.[18]

Thirty percent of children treated for brain tumors with cranial or craniospinal irradiation, with or without adjuvant cytotoxic chemotherapy, will develop thyroid dysfunction at some time after

treatment. The most frequent abnormality is compensated thyroid dysfunction. In a high proportion, thyroid function reverts to normal with time. It appears that the combined effect of direct irradiation to the thyroid gland during craniospinal irradiation plus cytotoxic chemotherapy is the most deleterious to the thyroid gland and is associated with the highest incidence of thyroid dysfunction and fastest time to onset of thyroid dysfunction.[18]

Treatment of Thyroid Dysfunction

In children with frank hypothyroidism, thyroxine replacement is indicated. Our policy has been to also treat with thyroxine those irradiated children with compensated thyroid dysfunction. The elevated TSH level returns to the normal range, which reduces the theoretical risk of thyroid cancer. Long-term thyroxine therapy is not without potential side effects, however, and we recommend that the requirement for thyroxine be reviewed periodically.

TESTICULAR FUNCTION

Low doses, 3 to 9 Gy, received as a scattered dose to the testes in 20 fractions over 4 weeks during the treatment of pediatric nephroblastoma resulted in oligospermia or azoospermia many years later.[19] Direct testicular irradiation with doses of 24 to 25 Gy completely ablated the germinal epithelium in all.[20] Leydig cell function is affected in most, as indicated by a low testosterone response to an acute bolus of human chorionic gonadotropin (HCG) and/or an increased basal plasma luteinizing hormone (LH) level. Leydig cell failure occurs soon after irradiation, with no evidence of recovery up to 5 years after irradiation. Most of these boys require androgen replacement to enable normal pubertal development to occur and to allow normal sexual function as adults.

Castillo et al[21] reported normal pubertal development following the use of 12- to 15-Gy doses of testicular irradiation for leukemia prophylaxis. Twelve of 13 subjects had normal basal testosterone levels and testosterone responses to HCG stimulation. However, all 7 boys for whom semen analysis was performed were azoospermic.

Lower doses of testicular irradiation may be received by boys undergoing TBI for a bone marrow transplant or scatter irradiation from spinal irradiation administered for some childhood brain tumors. The degree of damage to the germinal epithelium and Leydig cells is dependent on the radiation dose and the age and pubertal stage of the boy.[12,22]

OVARIAN FUNCTION

There have been few studies of ovarian function following irradiation uncomplicated by the effects of gonadotoxic cytotoxic chemotherapy.[23] Twenty-seven of 38 patients who received whole abdominal irradiation (20 to 30 Gy over 25 to 44 days) for various reasons in childhood failed to undergo complete pubertal development, and an additional 10 later developed premature menopause (median age, 23.5 years).[23] All had elevated follicle-stimulating hormone (FSH) levels and low estradiol levels. Sex steroid replacement was required to induce breast development and prevent subsequent osteoporosis.[19] Less well known is the lack of breast development, even with estrogen replacement, that was reported to occur in 5 of 38 of these patients. These required mammoplasty. In the same study, 15 patients received flank irradiation (20 to 30 Gy). Ovarian function was normal in 14. Three had breast asymmetry.

Morphologic studies following whole abdominal irradiation (20 to 30 Gy) have revealed marked inhibition of follicular growth and severe reduction in oocyte numbers.[24] Recent studies have indicated that the spinal component of craniospinal irradiation for the treatment of brain tumors and TBI before bone marrow transplantation may cause ovarian dysfunction due to radiation-induced ovarian damage.

RADIATION AND THE UTERUS

In women in whom ovarian function is preserved, but in whom the uterus has been involved in the radiation field, there is evidence that radiation to the uterus often results in failure to carry a pregnancy. In 38 women who received whole abdominal irradiation (20 to 30 Gy) during childhood, studied by Wallace et al,[23] there were 6 conceptions in 4 patients, all ending in second-trimester miscarriages. The majority of these 38 developed radiation-induced ovarian failure following whole abdominal irradiation. The uterine physical characteristics and blood flow were evaluated in some, as was the functional uterine response to exogenous sex steroid replacement.[25] Those who received whole abdominal irradiation in childhood had significantly smaller uteri in length than women with premature ovarian failure not attributable to irradiation. This implies that prepubertal exposure to irradiation may have an irreversible effect on uterine development and vasculature. In addition, the endometrium was unresponsive to physiologic serum levels of estradiol and progesterone, which were given by exogenous administration. Doppler signals from the uterine arteries were absent in most. It is unclear whether there is damage to the

vasculature of the uterus, although this is possible as appropriate vascularization and subsequent growth of the endometrium are essential for implantation and successful continuation of pregnancy. In summary, it is unlikely that women receiving a significant dose of abdominal irradiation in childhood will be able to sustain a pregnancy to term.

CONCLUSION

The progressive success of radiotherapy in curing various malignancies and/or prolonging life is accompanied by both destructive and stimulatory effects on the endocrine system. We now have adequate information regarding some of these effects to plan irradiation approaches to minimize damaging effects (eg, fractionated doses instead of single large doses) and to monitor the patients for developing endocrine disease. The endocrinologist and oncologist must form a therapeutic team to support the oncology patient.

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Abstracts From the Literature

Impaired Pubertal Growth in Acute Lymphoblastic Leukaemia

This extensive, long-term study of 182 children surviving acute lymphoblastic leukemia (ALL) focuses on their growth at the Hospital for Sick Children in London. The children were in first remission, had been off treatment for 2 years or more, and had attained the onset of puberty at the time of the study.

All had received cranial irradiation, usually given within 8 weeks of diagnosis: 2,400 cGy in 93 patients (before 1980, group A), and 1,800 cGy in the 89 others (group B). None had received spinal or gonadal irradiation. All patients were treated with standard chemotherapy, including intrathecal methotrexate in similar dosage regimens in either group. Mean ± standard deviation (SD) age at diagnosis or start of treatment was 4.8 ± 2.6 years in group A and 6.5 ± 3.3 years in group B. Patients who received growth hormone and/or an analogue of gonadotropin-releasing hormone were not included in the study, nor were those having dysmorphic syndromes or an abnormal karyotype.

Mean height at diagnosis or start of treatment was +0.29 standard deviation score (SDS) in group A, and +0.40 in group B. Mean final height was -0.63 SDS in group A, and -0.53 SDS in group B, the number of patients having reached final height being larger in group A (44 boys and 33 girls) than in group B (16 boys and 18 girls); the differences were not significant. There was a similar reduction in height SDS for age in both groups during the time of pubertal growth spurt, more important in girls (42 in group A, 47 in group B) than in boys, and also in patients treated before age 7 years than after this age.

The effect of cranial irradiation on the age at onset of puberty was studied in children treated not later than age 7 years. In group A, puberty started at 12.2 ± 1.0 years in boys and 10.6 ± 1.0 years in girls. In group B, surprisingly, it started significantly earlier; 11.4 ± 1.5 years in males and 9.9 ± 0.9 years in females ($P < 0.01$).

Uruena M, Stanhope R, Chessells JM, Leiper AD. *Arch Dis Child* 1991;66:1403-1407.

Editor's comment: *This long-term study of children who had undergone cranial irradiation for ALL is not the first but probably the most reliable, since the series of patients is particularly homogeneous, and the methodology for evaluation of growth and puberty particularly accurate. The results differ in some points from those reported in other series of cases. Without discussing these differences, we agree with the authors on their main conclusions, which are that: (1) a dose of 1,800 cGy impairs future growth as much as a dosage level of 2,400 cGy; (2) young age at irradiation is an important factor for later growth insufficiency; and (3) the severe impairment of final height in girls treated at less than 7 years of age probably results from a combination of growth hormone insufficiency and earlier puberty.*

These authors did not evaluate the possible effect or role of chemotherapy, which may play an adjunctive role to irradiation in producing growth retardation, as alluded to by Dr. Shalet in his article appearing in this issue.

Since patients who received hormonal treatment were excluded from the study, we await data on the long-term results obtained with growth hormone therapy in the follow-up and care of the survivors of childhood ALL, and then to comparison of their natural history as analyzed by the present study.

Jean-Claude Job, MD

2nd Editor's comment: *The data in this abstract, and Dr. Job's comments, complement the presentation by Dr. Shalet carried as one of the lead articles in this issue. Age, sex, chemotherapy, and irradiation dose are variables that probably help determine the ultimate height of children treated for ALL with irradiation. Rereading the section regarding ALL in Dr. Shalet's article may be useful.*

Robert M. Blizzard, MD

Hemihypertrophy, Uniparental Disomy, and Risk for Cancer Or: Chromosome 11 Uniparental Isodisomy Predisposing to Embryonal Neoplasms

Grundy et al report on a child with hemihypertrophy and congenital adrenal carcinoma in whom Wilms' tumor subsequently developed. It has been known for some time that Wilms' tumor is associated with the inactivation of both alleles of a tumor-suppressor locus on chromosome 11p. Tumor-specific loss of 11p15 sequences also has been demonstrated in adrenal carcinoma. The overgrowth disorder Beckwith-Wiedemann syndrome is associated with the development of Wilms' tumor and other cancers, and it also has been shown to be associated with loss of the same portion of chromosome 11, either through deletion or uniparental disomy (2 copies of chromosome 11p from father). It is always the maternal copy of chromosome 11p that is lost. These results prompted Grundy et al to examine chromosome 11 in this case of hemihypertrophy with Wilms' tumor.

Molecular genetic analysis revealed that the child had a normal-appearing karyotype. However, when restriction fragment length polymorphism (RFLP) analysis was done, it became apparent that he had uniparental paternal isodisomy for chromosome segments 11p13 and 11p15 (ie, both chromosome 11p segments came from the father). This supports the theory that these segments of chromosome 11 are imprinted, ie, they are differentially expressed when inherited from the mother as opposed to the father, and that they play some role in tumorigenesis. (However, because the child had inherited 2 copies of the same chromosome 11, rather than 1 copy from each parent or 2 different chromosomes from the father, it is also possible that the father carried a mutant recessive tumor-suppressor gene and that the absence of a balancing normal allele in the child has revealed this mutation.) Because the child also had normal kidney and adrenal tissue, the authors conclude that isodisomy cannot represent the final event responsible for oncogenic transformation. Thus, inactivation of an 11p tumor-suppressor locus seems insufficient to cause Wilms' tumor, which they conclude must be a multistep disorder.

The authors comment that their case, with hemihypertrophy and tumors as the only phenotypic abnormality, may or may not represent an incomplete form of Beckwith-Wiedemann syndrome. But it does demonstrate that this type of chromosome 11 aberration can be present without expression of the complete syndrome.

Grundy P, Telzerow P, Paterson MC, et al. *Lancet* 1991;338: 1079-1080.

Editor's comment: *In addition to providing further support for the theory of genomic imprinting, this case also shows us that patients with hemihypertrophy may carry uniparental disomy for particular chromosomal segments, and that this can cause loss of tumor suppression and increase the risk of these patients for developing malignant tumors. These observations may provide a means of identifying those patients with hemihypertrophy who are at risk for malignancy.*

Judith G. Hall, MD

Stimulation of Collagen Synthesis and Linear Growth by Growth Hormone in Glucocorticoid-Treated Children

In this study, the collagen synthesis and insulin-like growth factor 1 (IGF-1) status before and after growth hormone (GH) treatment in children on chronic glucocorticoid (GC) therapy was investigated. Seven children with the following diagnoses were studied: autoimmune colitis, eosinophilic fasciitis, asthma, nephrotic syndrome, and renal transplant recipients for obstructive uropathy, hypoplastic kidneys, or focal segmental glomerulosclerosis. The chronologic age of the patients was between 8 3/12 and 15 7/12 years, the bone age was <10 years for girls and <12 years for boys, and the Tanner staging was prepubertal for all except for one girl, who was Tanner stage III. All had subnormal growth velocity for at least 6 months prior to the study while on stable dosages of GC. Height, weight, IGF-1 activity, glycosylated hemoglobin level, and C-terminal type 1 procollagen levels were measured at baseline and every 3 months thereafter following the initiation of treatment with recombinant human GH (0.3 mg/kg/wk) for 6 to 21 months (mean, 13.1 ± 4.9 months). Skeletal maturation and 2-hour postprandial serum glucose and insulin levels were assessed every 6 months. All patients showed increased growth velocity during treatment with GH. Mean growth velocity increased from 3.43 ± 0.65 cm/yr to 6.72 ± 0.84 cm/yr with GH therapy ($P<0.005$). SDSs corrected for bone age ($P<0.005$), IGF-1 levels ($P<0.005$) and C-terminal type 1 procollagen levels ($P<0.005$) also increased with GH therapy. C-terminal type 1 procollagen levels correlated well with growth velocity ($r=0.652$), while IGF-1 levels did not ($r=0.17$). Glycosylated hemoglobin levels rose during GH treatment. It was felt that since no child experienced significant improvement in his or her underlying illness or puberty stage, and since glucocorticoid dosages changed little during the study period (never decreasing below the baseline dose in 6 of 7 children), the improvement in GV and type 1 collagen synthesis noted were likely the result of GH treatment. It was concluded that both inhibition of IGF-1 effects and collagen synthesis were responsible for the growth-retarding effects of GC therapy.

Allen DB, Goldberg BD. *Pediatrics* 1992;89:416-421.

Editor's comment: *This study appears to show benefits of GH treatment. It promoted growth and procollagen synthesis in children on long-term GC therapy. This study also offers a biochemical explanation for stunted growth due to GC treatment and for increased growth velocity with GH therapy. This study appears to support the hypothesis that impaired linear growth and skeletal maturation associated with chronic GC therapy results from: (1) inhibited IGF-1 activity and (2) impaired type 1 procollagen synthesis. Additionally, GC may suppress GH secretory response to GH-releasing hormone, but this was not measured by the authors. Each mechanism could potentially be improved by exogenous GH treatment if sufficient dosages are given to overcome these 3 competitive effects of GC. However, the data differ from that reported many years ago by other investigators who showed that GH had no beneficial effects on GC-treated children (*J Clin Invest *1968;47:436-491). We also have treated several patients with corticosteroid-dependent asthma on GC therapy, and they showed marked improvement in growth after GH therapy. However, the effects of GH therapy were related to the dose of GC given while GH treatment was ongoing (presented at the 73rd Annual Meeting of the Endocrine Society, June 19-22, 1991; abstract No. 1315). GH treatment at the dosage usually employed for treatment of hypopituitarism or for Turner syndrome patients could not overcome the effects of pharmacologic doses of GC.*

It is difficult to ascertain from the studies reported by Allen and Goldberg whether improvement in disease activity (not quantitated) and/or alternate-day GC treatment resulted in catch-up growth coincidentally with GH therapy in their patients. Five of 7 patients received 15 to 50 mg/m²/d hydrocortisone equivalent on an alternate-day regimen, and the remaining 2 patients received only a physiologic dose of 15 mg/m² hydrocortisone equivalent.

*The exact amount of GC administered on alternate days necessary to inhibit and/or allow growth is not known. The effect of alternate-day GC treatment on growth was studied by Whittington et al in patients with Crohn's disease (*Gastroenterology *1977;72:1338-1344). In that study, the dose of prednisone given was from 52.5 to 157.5 mg/m²/d of hydrocortisone equivalent. Despite these pharmacologic doses, the patients showed catch-up growth when GC was given every other day.*

*In this study, the normal or elevated pretreatment values of IGF-1 were attributed, in part, to the obesity and/or hyperinsulinemia found in many GC-treated patients. Dissociation of serum GH and IGF-1 levels in obese individuals might result from insulin-mediated IGF-1 production and consequent suppression of GH secretion (*J Clin Endocrinol Metab *1976;42:370-378 and* Endocrinology *1979;73:209-213). Further, it was previously shown that within hours of oral GC administration, IGF-1 activity falls precipitously while IGF-1 levels remain unchanged (*J Clin Endocrinol Metab *1985;61:618-626). This inhibitory effect was reflected by the GC-induced stimulation/potentiation of circulating IGF-1 inhibitors. Thus, while IGF-1 levels rose with GH therapy in these patients, the poor correlation with growth velocity was not surprising.*

*The potential beneficial effects of GH treatment in patients receiving GC need to be considered in relation to increasing the risk of side effects when patients are treated with these 2 antagonistic drugs. Particular attention needs to be given to the administration of large doses of GH, which may be needed to overcome the pharmacologic effects of GC. This would potentiate carbohydrate intolerance as well as increase other potential toxicities. Thus, undertaking a trial with GH in growth-inhibited patients receiving GC without an investigative protocol is strongly discouraged. There may be other treatments of potential value to enhance growth while controlling the primary disease that may be of help in corticosteroid-dependent patients, ie, corticotropin therapy. (*Acta Paediatr Scand *1990;79:77-83).*

Fima Lifshitz, MD

Osteopenia in Growth Hormone-Deficient Adult Males and Men With Constitutional Delayed Puberty

Finkelstein et al determined bone mineral density in a cohort of 23 men (age 26 ± 2 years) who had a history of delayed pubertal development and who had presented to the Pediatric Endocrine Clinic of Massachusetts General Hospital between 1974 and 1980. Each had a history of the onset of puberty after age 15 years and also a history of height at or below the 5th percentile for chronologic age before the pubertal growth spurt. The findings were compared with those determined in a control group of 21 men (age 24 ± 3 years) who had a history of puberty beginning before 14 years of age. Control subjects at the time of the study were 2 years younger than those in the study group in order to match the groups for duration of exposure to adult levels of gonadal steroids. Forearm bone mineral density was determined by single-photon absorptiometry, and spinal bone density was determined by dual energy X-ray absorptiometry of the first through fourth lumbar vertebrae.

Bone mineral density was significantly lower in the men who had experienced delayed puberty. Multivariate analysis of variance demonstrated that the timing of puberty remained a significant determinant of bone density after accounting for the effects of age, body mass index, exercise, alcohol intake, calcium intake, and serum testosterone. The authors conclude that their data are consistent with the hypothesis that the timing of puberty is an important determinant of peak bone mineral density in male.

Kaufman et al measured bone mineral content by photon absorptiometry in 30 men (age 26.5 ± 1.2 years) with growth hormone deficiency (GHD) (8 with isolated GHD and 22 with multiple pituitary deficiencies) and compared the results with those from 30 male controls of similar age, weight, and body mass index. Bone mineral content was measured at the distal third of the nondominant forearm (proximal site) and close to the carpal joint (distal site) of the same forearm by single photon absorptiometry. Bone mineral content of the lumbar spine (L2 to L4) was determined with dual-photon absorptiometry. All subjects with GHD had received growth hormone (GH) replacement therapy and had reached adult bone age. GH treatment had been interrupted for at least 6 months, but other hormonal replacement was continued. Bone mineral content was significantly lower at both the forearm and the lumbar spine in the subjects with pituitary hormone deficiencies. This was true regardless of whether there were single or multiple hormonal deficiencies. A 6- to 28-month prospective evaluation of 19 subjects showed no subsequent bone loss. The authors conclude that adult men with childhood GHD have a significant bone mineral deficit as compared with age- and weight-matched controls.

Finkelstein JS, Neer RM, Beverly MK, et al. Osteopenia in men with a history of delayed puberty. *N Engl J Med* 1992;326:600-604.

Kaufman JM, Taelman P, Vermeulen A, Vandeweghe M. Bone mineral status in growth hormone-deficient males with isolated and multiple pituitary deficiencies of childhood onset. *J Clin Endocrinol Metab* 1992;74:118-123.

***Editor's comment:** These 2 papers should be read together. The methodology for each is similar as are the findings. Kaufman et al show that individuals with GHD have lower bone mineral density at adulthood than controls, but they do not exclude the possibility that some of the deficit observed is due to an associated androgen deficiency. Indeed, the majority of their subjects have gonadotropin deficiency. Finkelstein et al conclude that since the only known physiologic abnormality in their subjects is a delay in the onset of puberty, this transient delay in gonadal steroid secretion is important to achieving peak bone mineral density during adolescence. However, Finkelstein's subjects had both delayed puberty and constitutional delay of growth. These patients were at or below the 5th percentile for age and their height before the pubertal growth spurt was at least 3 standard deviations below the mean. Since it is known that gonadal steroids increase GH pulse amplitude during puberty, it is possible that the decrease in bone mineral content associated with pubertal delay is secondary to a relative GH insufficiency during early adolescence. Neither study reported an increased incidence of bone fractures in adults with either GHD or delay of puberty. Such data would be exceedingly important in demonstrating the significance in the findings of either paper. Both authors suggest that their data support a role for early therapy with either androgen supplementation in boys with delayed puberty or GH treatment of males with hypopituitarism.*

William L. Clarke, MD

Abnormalities of Insulin-Like Growth Factor (IGF-1 and IGF-2) Genes in Human Tumor Tissue

The structure and expression of genes coding for insulin-like growth factors 1 and 2 (IGF-1 and IGF-2) were investigated in tissue samples from 37 human tumors: 5 with severe hypoglycemia of 1.85 ± 0.7 mMol/L (range, 0.9 to 2.7 mMol/L), including pleural fibroma, leiomyoma, leiomyosarcoma, lymphosarcoma, and exocrine pancreatic carcinoma; and 32 without known hypoglycemia, including cancers of breast, kidney, and lung (n=17); liver (n=4); Conn's adenoma (n=3); thymoma and pheochromocytoma (n=3); hepatic metastases of 1 pancreatic and 1 colon carcinoma; and 3 embryonic tumors (nephroblastoma, neuroblastoma, and adrenocortical carcinoma). The tumor tissues were removed from patients at surgery, immediately frozen, and stored at -80°C until biochemical study. Blood samples for extraction of DNA from blood nucleated cells also were obtained from patients.

Three established human tumoral cell lines were studied for comparison: 1 from hepatoma, 1 from colon carcinoma, and 1 from neuroblastoma. Genomic DNA and total RNA were extracted by grinding of frozen tissue samples, separation, and purification.

Specific human genomic DNA probes were used after labeling with α^{32}P-ATP.For IGF-1, it was a 667-bp *Eco*RI-*Bam*HI fragment containing the coding region with exons 1,2,3, and 5 between a 163 bp 5' untranslated region and a 44-bp 3' untranslated region. For IGF-2, the coding region was associated with a 99 bp chain from the 3' untranslated region (exons 7,8, and 9) and a 15 bp chain from the 5' untranslated region. A human insulin 2.7-kb DNA fragment and a human calcitonin 827-bp cDNA probe also were used as controls. Analysis was performed by Southern blot.

The extent of DNA methylation was evaluated by comparison between restriction profiles obtained with *Ava*II and with other restriction enzymes.

RNA from the samples was studied by northern blot and dot blot methods. Expression of RNA was evaluated on the basis of densitometric analysis, compared with that obtained from normal human adult liver fragments taken as reference samples.

No obvious rearrangement such as deletion or amplification of IGF genes was observed in any of the tumor samples investigated. But the extent of DNA methylation of IGF genes and the level of mRNA expression were extremely variable among these tumoral tissues.

A relationship could be detected between gene demethylation and IGF overexpression in the 5 tumors associated with hypoglycemia: 2 with a great degree of gene demethylation and overproduction of IGF-1 and IGF-2 mRNA, 1 with slightly demethylated IGF-2 gene and large amounts of the corresponding mRNA, and 2 without demethylation or expression of IGF genes.

In the other tumor samples studied, those not associated with hypoglycemia, no IGF-1 demethylation was found. IGF-2 gene demethylation and mRNA expression were highly variable. No relationship was evident.

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In the 3 human carcinomatous cell lines analyzed, there was high expression of IGF-2 mRNA without IGF-2 gene demethylation. None expressed any detectable IGF-1 mRNA, although the IGF-1 gene was extensively demethylated in the neuroblastoma-derived cells.

Loss of heterozygosity was found in 3 children with tumor, using parallel investigation of tumoral and normal cells. Family study was possible in 2 and revealed a decrease of the maternal allele for IGF-2 gene. By using an insulin probe, it was shown that in the case of nephroblastoma the allele loss was not IGF-2-specific but extended to a large section of the 11p15 region. In adult patients, no loss of heterozygosity was found in tumor samples or in the blood nucleated cells analyzed. However, an imbalance of the 2 IGF-2 alleles was found in 2 breast and 2 liver carcinomas, raising questions about some role in specific demethylation and expression.

The authors' first conclusion is that in tumors in which IGF-1 and IGF-2 mRNAs are overproduced, there is no detectable DNA deletion or amplification; however, there may exist specific IGF gene demethylation. The second conclusion is that, although embryonic tumors show a loss of heterozygosity in the IGF-2 gene, a different mechanism seems responsible for IGF-2 mRNA overexpression in certain adult tumors.

Schneid H, Seurin D, Noguiez P, Le Bouc Y. *Growth Regulation* 1992;2:45-54.

Editor's comment: *This extensive work investigates at the genomic level the existence and possible role of IGFs in different types of human tumors, also aiming to determine whether a relationship exists between the tumorigenesis and the structure and expression of IGF genes. The extreme diversity of results suggests that there is no clear or constant relationship between any of the tumoral types or lines studied and abnormalities of IGF-1 and IGF-2 genes or their expression. However, 2 possibly important facts appear. One is the relationship between IGF overexpression and gene demethylation found in tumors associated with hypoglycemia. The second is the confirmation, in some childhood tumors, of a loss of heterozygosity in the 11p15 region coding for IGF-2, completed by demonstration of an imbalance of maternal origin in the corresponding leukocyte alleles. This is a new piece in the complicated field of relationships between IGFs and cancer growth.*

Jean-Claude Job, MD

2nd Editor's comment: *This abstract, the abstract on page 12 entitled "Hemihypertrophy, Uniparental Disomy, and Risk for Cancer," and the abstract entitled "Uniparental Disomy in Beckwith-Wiedemann Syndrome," published in* GGH *Vol. 8, No. 2 are interrelated. Chromosome 11 imprinting and disomy seem to be key, but the issues are more complex. Intriguingly, Beckwith-Wiedemann syndrome is characterized by hypoglycemia (probably IGF-1 induced), tumor formation such as Wilms' tumor in high frequency, and overgrowth (possibly a function of IGF-1 or IGF-2). The 11p15 and 11p13 areas have the associated genes to produce the phenomena addressed in these 3 articles. Gene demethylation also appears to play a role—particularly in relation to IGF-1 gene demethylation.*

Robert M. Blizzard, MD

Reproducibility of 24-Hour Growth Hormone Profiles in Children

The rate of growth hormone (GH) secretion and the pattern of GH peaks were compared in a group of 9 children during their prepubertal period in repeated 24-hour GH profiles. At investigation, the children were 6 to 13 years old (at first profile, 6 to 11 years old) and of normal height (± 2 standard deviations [SD]). Two profiles were obtained per child, with a mean time interval of 1.5 years (range, 0.7 to 3.5 years). The calculated GH secretions of the first and second profiles were compared. As a group, no significant differences were obtained in secreted amount of GH, when the data from second profile was expressed as a percentage of data from the first profile (93% ± 8%), number of peaks (95% ± 7%), or mean peak amplitudes (92% ± 11%). Between the repeated curves of an individual child, maximal difference in secretion, number of peaks, and mean peak amplitudes ranged around ·30%, with a mean intraindividual coefficient of variation of 12%. The reproducibility in the peak distribution for all profiles was also analyzed. Reproducibility of the temporal pattern of profiles was analyzed using time-series analysis (Fourier analysis) and showed no difference in rhythmicity between the different occasions.

In conclusion, a high reproducibility of both GH secretion and GH pattern was found for the whole group of prepubertal children. The high degree of reproducibility of the 24-hour GH profiles of the entire group indicated that the information from these curves, in terms of both pattern and total secretion, can be used for clinical as well as for physiologic purposes. The intraindividual reproducibility was less pronounced, however, leading to a sound skepticism when relating biologic phenomena to a single profile of an individual child.

Albertsson-Wikland K, Rosberg S. *Acta Endocrinol* 1992; 126:109-112.

Editor's comment: *The reproducibility of measurements of GH secretion has been studied and questioned in many previous papers. This study deserves exceptional consideration since it uses extremely accurate methodology and gives all the technical data, including variability of the results of plasma GH radioimmunoassays. The authors conclude that there is a contrast between the excellent overall reproducibility in recording of 24-hour GH secretion in groups of subjects, and these data can be used for clinical and physiologic purposes. However, the extent of individual variations prompts skepticism about interpreting a single profile in an individual child.*

Jean-Claude Job, MD

2nd Editor's comment: *Martha et al did a similar extensive study that was presented at the American Endocrine Society Meeting in San Antonio in June 1992, under the title "Physiological GH Release is Regulated Over Time Within Characteristic, Individually Determined Limits Which Vary Predictably, But Reciprocally, With Body Mass Index." These authors performed 44 integrated studies in 9 prepubertal, normal-statured boys over 9- to 35-month periods. Among the group data, mean 24-hour integrated concentrations of GH for the individual profiles spanned a 6-fold range (1.1 to 7.0 ng/mL) with an intersubject CV of 46%. In contrast, values of individual subjects exhibited much less variability (mean CV, 26% ± 4%). Therefore, each individual was consistent in having low, medium, or high integrated GH concentrations, and the mean ICGH level in each of these normal boys correlated strongly and inversely with body mass index (BMI) SD scores.*

The authors conclude that during late prepuberty (9 to 12 years of age, Tanner stage I): (1) individual boys regulate daily GH secretion within relatively confined limits, which are characteristic for that individual and much narrower than the broad range present in the larger population; (2) differences in BMI help determine the GH secretion range which characterizes, and is therefore "normal" for, each individual; (3) differences in mean 24-hour GH levels among normally growing boys arise primarily from differences in GH pulse size; and (4) there is no consistent progressive change in mean 24-hour GH release in prepubertal boys before puberty occurs.

In correlation with the paper by Albertsson-Wikland and Rosberg, there is a variation in GH secretion within an individual in respect to quantity, which may vary as much as 75% to 100% between 2 profiles. However, the mean data for the group between profiles is much less variable. In addition to the data presented from Sweden, Martha et al determined that children have significantly different GH secretion from each other on the basis of BMI. GH secretion and BMI vary inversely.

Robert M. Blizzard, MD

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Effects of Drugs and Other Chemicals on Fetal Growth

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Prenatal exposure to a number of chemicals can cause growth retardation in humans. Some of these agents also may produce permanent alteration of structure or function and thus are considered to be teratogens.[1] Although most human teratogens are associated with fetal growth retardation, some are not. There also are several agents that can cause fetal growth retardation but are not recognized as human teratogens.

Fetal growth retardation is regularly associated with maternal diseases such as hypertension and severe diabetes mellitus.[2] Growth retardation is a cardinal feature of the embryopathies that result from intrauterine infection with toxoplasmosis, rubella, cytomegalovirus, syphilis, and varicella.[3] Similarly, exposure to high doses of ionizing radiation during embryonic development regularly leads to permanent growth deficiency, microcephaly, and mental retardation.[4] These human teratogens will not be discussed in this paper, which is restricted to consideration of the effects of drugs and other chemicals.

While we usually speak of "teratogens" as if teratogenicity were a property of chemistry alone, it is important to remember that the dose, route, and timing of exposure are as important as the nature of the chemical itself in creating a teratogenic risk. Recognized "human teratogens" are agents for which sufficient conditions of exposure are encountered to produce a teratogenic effect. Studies in experimental animals suggest that many other agents also would have teratogenic potential in humans if sufficient exposures were encountered.

The same principle no doubt applies to agents that cause growth retardation but not teratogenic effects. The agents that we recognize as having such properties are encountered by pregnant women in doses and circumstances sufficient to permit the growth-retarding effects of these chemicals to be expressed. It seems likely that many other chemicals would have similar potential if sufficient exposure occurred.

MEDICATIONS THAT ARE TERATOGENS

Aminopterin is a folic acid antagonist. It has been administered to pregnant women to induce abortion. A related drug, methotrexate, is used as an antineoplastic agent. A rare but strikingly similar pattern of congenital anomalies has been observed among children born after exposure to aminopterin during embryogenesis.[5] Frequent features of this syndrome include growth retardation, delayed calvarial ossification, craniosynostosis, hydrocephalus, abnormal auricles, ocular hypertelorism, micrognathia, and cleft palate. Although developmental delay is seen during childhood, the few affected adults who have been

In This Issue

reported appear to have normal intelligence or only mild mental retardation.

Congenital anomalies have been observed with increased frequency among the children of epileptic women treated with anticonvulsants during pregnancy. This association has been observed with various medications, including trimethadione, phenytoin, valproic acid, and carbamazepine. It is difficult to determine from available data to what extent this increased risk is attributable to the agents themselves as opposed to the seizure disorder or some factor that predisposes to seizures. A characteristic pattern of congenital anomalies, ie, a fetal anticonvulsant syndrome, has been reported with each of these agents.[6-11] Frequent features include growth and developmental retardation and unusual facies (Table 1 and Figure 1A). Although the syndromes associated with all of the anticonvulsants are similar, some features are more commonly encountered with maternal use of a particular agent. For example, distal digital and nail hypoplasia are an especially frequent feature of the fetal phenytoin syndrome (Figure 1B) and spina bifida is most often seen with the fetal valproic acid syndrome.

A characteristic pattern of congenital anomalies has been observed in children born to women treated with warfarin during pregnancy.[12] Frequent features of this "warfarin embryopathy" include nasal hypoplasia (Figure 2), stippled epiphyses on radiographs, and growth retardation. No adequate epidemiologic study of pregnancy outcome in women treated with warfarin is available, but on the basis of published experience (an obviously biased sample), it has been estimated that about 10% of infants born alive to mothers who take warfarin during pregnancy have warfarin embryopathy. Maternal heparin use in gestation has been associated with stillbirth and other complications of pregnancy, but this drug does not cross the placenta.[12]

Captopril and enalapril are antihypertensive agents that act by inhibiting angiotensin converting enzyme. Although maternal treatment with these drugs during early pregnancy is not known to damage the embryo, treatment late in pregnancy is associated

Figure 1A
A child with typical features of fetal phenytoin syndrome

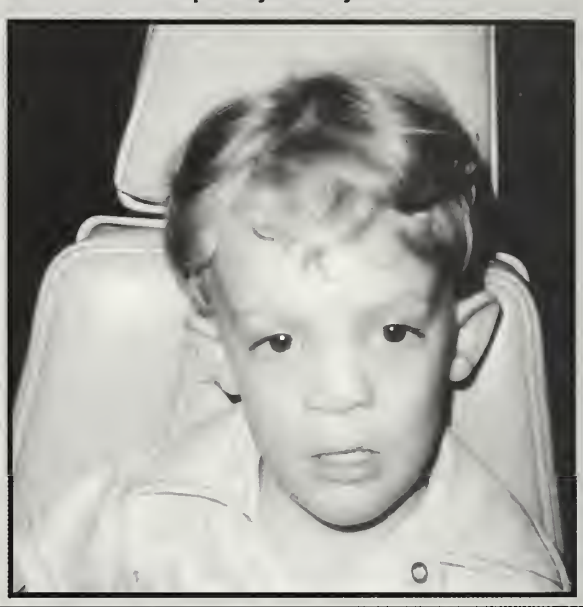


Table 1
Features of Fetal Anticonvulsant Syndromes

May be seen with various anticonvulsants:
- Growth deficiency
- Developmental delay
- Midface hypoplasia
- Short nose with broad or flat bridge
- Epicanthal folds
- Micrognathia
- Congenital heart defects
- Urogenital anomalies

Associated more with one particular anticonvulsant than with others:
- Spina bifida (valproic acid)
- Distal digital hypoplasia (phenytoin)
- Nail hypoplasia (phenytoin)
- Tracheomalacia (valproic acid)
- Talipes equinovarus (valproic acid)

Figure 1B
Nail hypoplasia is a frequent manifestation of fetal phenytoin syndrome

with a substantial risk of fetal growth retardation, oligohydramnios, anuria, and perinatal death.[13]

Recreational Agents and Drugs of Abuse

A pattern of congenital anomalies called the fetal alcohol syndrome occurs in infants born to women with chronic alcoholism during pregnancy.[14,15] This topic was previously reviewed in *GROWTH, Genetics & Hormones* (1988;4[1]:1-3). Prenatal and postnatal growth retardation are characteristic features of this syndrome, and microcephaly is frequent. About 80% of children with severe fetal alcohol syndrome have measured lengths and weights <2 standard deviations (SD) of that expected. Other manifestations include mental retardation, hyperactivity and other behavioral disturbances, poor coordination, and typical facial appearance (Figure 3, page 4). Congenital heart disease and brain malformations are common, but other major congenital anomalies are infrequent. Lower amounts of maternal alcohol consumption during pregnancy (2 to 4 mixed drinks, beers, or glasses of wine per day, on the average) have been associated with milder growth deficiency, intellectual deficits, and behavioral abnormalities.[16,17]

Fetal growth retardation and spontaneous abortion occur with increased frequency among pregnant women who are heavy cigarette smokers.[18,19] Low birth weight is associated with maternal smoking in a dose-related fashion. This effect seems to be due primarily to fetal growth retardation rather than to prematurity. Controversy exists regarding whether the low birth weight seen among infants of women who smoke during pregnancy is caused by smoking or by the other correlated factors. The preponderance of evidence favors the former view. Maternal cigarette smoking may account for up to 40% of fetal growth retardation in advanced countries.[20] Persistent mild reduction of growth and intellectual performance has been observed among the children of women who smoked during pregnancy. Some studies suggest that birth weight also is decreased slightly among the children of nonsmoking women exposed to tobacco smoke in their environment.

The frequency of spontaneous abortion is 20% to 80% higher than expected among women who smoke cigarettes during pregnancy.[18] The risks appear to be greater for heavy smokers than for light smokers. Some studies, but not others, suggest that perinatal mortality and other complications of pregnancy also may be increased among the infants of women who smoke cigarettes during pregnancy. Congenital anomalies do not appear to be unusually frequent among the children of women who are heavy smokers.

An association between maternal coffee drinking during pregnancy and low birth weight has been observed consistently in epidemiologic studies,[21,22] but in many instances this association is largely due to confounding effects of maternal cigarette smoking. Maternal coffee drinking during pregnancy does not appear to affect the risk of congenital anomalies among the offspring.

Intrauterine growth retardation, perinatal death, and a variety of other perinatal complications have frequently been observed among the children of narcotic-addicted mothers,[23,24] but it is unclear whether these effects are due to fetal exposure to narcotics or to the generally poor health of these women. Subsequent growth of their children appears to be normal in most cases. Malformations are not usually frequent among the infants of narcotic-addicted mothers.

Maternal cocaine use during pregnancy is associated with an increased risk of placental abruption and possibly of congenital anomalies due to vascular disruption.[25] Growth retardation involving weight, length, and head circumference has consistently been noted among infants born to women who use cocaine during pregnancy, but a causal relationship is difficult to establish because of the presence of many confounding factors in these women.

Figure 2
Nasal hypoplasia and iris dysgenesis in a child demonstrating the effects of warfarin embryopathy

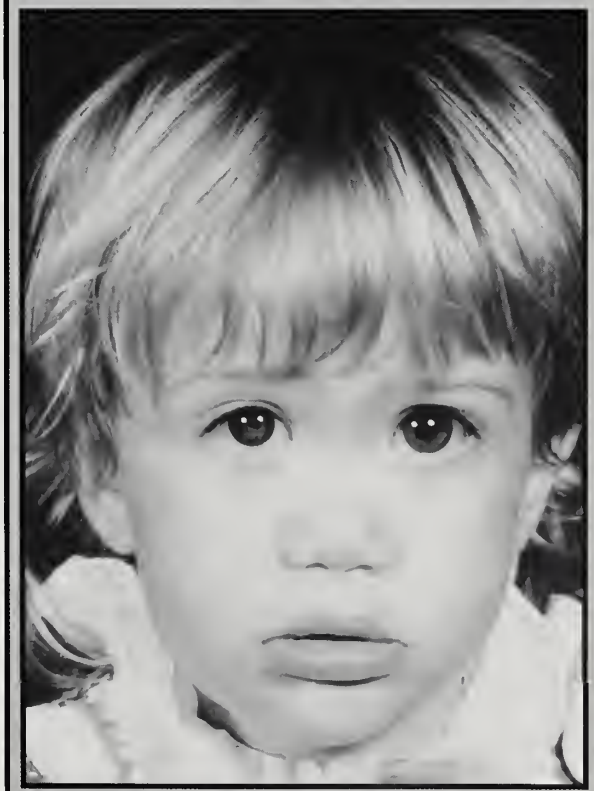
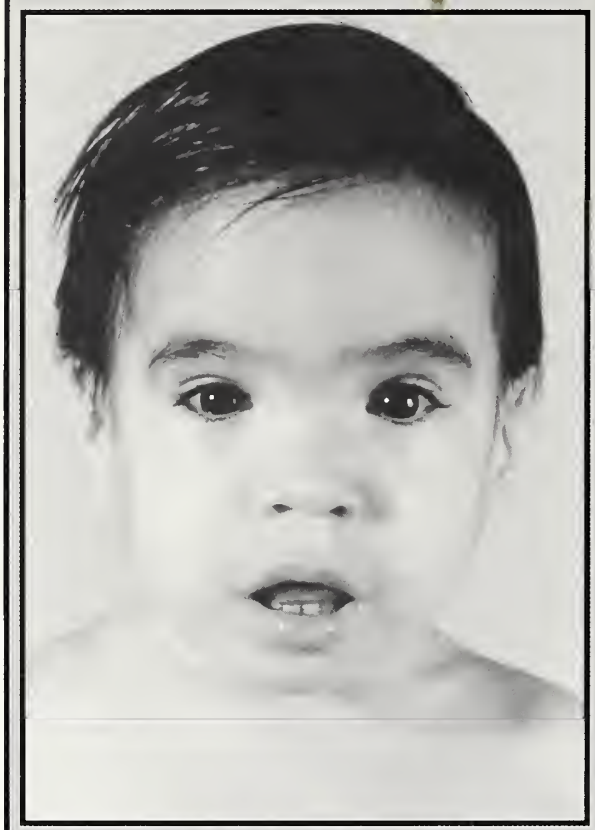


Figure 3
Facies in fetal alcohol syndrome



(From Little RE, Streissguth AP. Alcohol, pregnancy, and the fetal alcohol syndrome. In: *Alcohol Use and Its Medical Consequences: A Comprehensive Teaching Program for Biomedical Education*. Project Cork of Dartmouth Medical School. Timonium, Md: Milner-Fenwick, Inc.; 1982.)

Maternal inhalation of large amounts of toluene to "get high" during pregnancy may produce growth deficiency, developmental delay, behavioral abnormalities, and minor physical anomalies among the offspring.[26] Women who use toluene in this way often suffer toxic manifestations themselves.

OCCUPATIONAL AND ENVIRONMENTAL EXPOSURES

Although much concern has been raised about the potential adverse effects of exposure to occupational or environmental chemicals during pregnancy, only 2 exposures of this type (PCBs [polychlorinated biphenyls] and methyl mercury) have convincingly been shown to cause fetal growth retardation in humans. Skin discoloration and growth retardation have been noted among the infants of pregnant women who ate cooking oils that were highly contaminated with PCBs.[27] Less pronounced effects on fetal growth have been observed among the children of mothers who ate PCB-contaminated Great Lakes fish or were exposed to PCBs in the workplace. Brain damage and consequent cerebral palsy have been seen among the children of pregnant women who ate food that was heavily contaminated with methyl mercury.[28] The frequency of low birth weight correlates with maternal and neonatal blood methyl mercury concentrations in populations whose food supply is contaminated with these compounds.[29]

PATHOGENIC MECHANISMS

Many processes are involved in normal fetal growth, and interference with any of these processes could result in fetal growth retardation. Cell death or altered cell growth and proliferation are probably important factors in the growth retardation produced by radiation and chemicals such as aminopterin. Fetal vascular compromise, either directly or indirectly by means of an effect on the placenta or maternal vasculature, seems likely to be important with agents such as cigarettes, captopril, and cocaine. Some agents may lead to fetal growth retardation through a combination of effects involving the placenta as well as embryonic or fetal cell proliferation, growth, and death. Alcohol is probably one example.

PREVENTION OF FETAL GROWTH RETARDATION

Familial factors appear to be the single most important predisposition to fetal growth retardation,[20] but pharmacologic approaches may provide an effective means of prevention in such cases. A recent randomized controlled trial of maternal treatment with low-dose aspirin in the second and third trimesters of pregnancy demonstrated a 225g improvement in birth weight among the infants of women who had had a prior pregnancy complicated by fetal growth retardation, stillbirth, or placental abruption.[30] The beneficial effect was most marked among women who had previously had 2 or more poor pregnancy outcomes. The mechanism by which aspirin improves fetal growth in these high-risk pregnancies is unknown but may involve effects on placental prostaglandins.

Avoidance of cigarette smoking, alcohol drinking, and drug abuse during pregnancy would likely prevent at least 40% of all cases of fetal growth retardation.[20] Many spontaneous abortions, fetal deaths, and other adverse pregnancy outcomes also would be avoided if pregnant women did not use these agents. Despite the importance and apparent simplicity of this approach, it has been difficult to effect in practice. Many of these agents are addictive, and their use is a component of

patterns of social interaction that are very difficult to change. Public education and universal availability of early prenatal care provide the best opportunities for reducing cigarette smoking, alcohol drinking, and drug abuse among pregnant women.

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Recent Developments in the Study of the Psychosocial Aspects of Short Stature

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While enhanced growth velocity is the well established benefit of GH therapy, potential psychosocial benefits have been suggested by studies of clinical samples of short children. Conclusions based on these early studies are drawn into question because of small samples, diagnostic heterogeneity, and a lack of control observations. Emerging studies, using more sophisticated new research designs, are beginning to challenge and refine the conclusions of earlier reports.

A glimpse of this new wave of studies was recently provided to participants of the Fourth North Coast Conference of the Society of Pediatric Psychology. The meeting, held April 23-26 in Buffalo, New York, included a symposium on the psychosocial aspects of short stature. The studies described focused upon the behavioral adjustment of 4 different populations of children and adolescents with short stature: (1) those in the general population who had not been referred for an evaluation of their growth or height; (2) clinically referred individuals prior to any treatment; (3) those who had received GH; and (4) GH-treated girls with Turner syndrome (TS).

Dr. Michael Vance of the Creighton Medical School in Omaha, Nebraska, reported on a study that investigated the association of short stature to psychological adjustment in children in the general population; a reanalysis of data from cycles II (ages 6 to 11 years; n=7119) and III (ages 12 to 17 years; n=6768) of the National Health Examination Survey. Measuring such factors as school adjustment, peer relations, aggression, immaturity, and anxiety, Dr. Vance found only very subtle (although statistically significant) differences between children that could be accounted for by their height. Also, change in growth rate over approximately 4 years (as assessed in a subsample of 2177 children) was unrelated to the measures of positive adjustment. These relationships were maintained across subsamples 1 to 3 standard deviations (SD) below the mean for height norms. This study is the only large-scale survey of the relationship between height and psychological functioning conducted in the United States. It suggests that short children in the general population function socially and academically in ways that are reasonably indistinguishable from that of average-statured peers. Based on these findings, Dr. Vance suggested that GH therapy to increase stature for psychosocial reasons is not indicated.

Dr. David E. Sandberg of Children's Hospital of Buffalo reported on the results of a psychosocial screening of 150 children and adolescents consecutively referred to endocrinologists for evaluation of growth and height. The screening, a routine component of the initial endocrine visit, included a brief psychosocial assessment of the patient based on information collected from the parent(s) and the child. The mean standardized height for the group was -2.3 SD, with a range of -4.0 to -1.6 SD. The majority of boys (n=101) and girls (n=49) reported that they were teased because of their size relative to their chronologic age. Parents confirmed these reports. Despite these common stresses, this clinically referred group appeared to be functioning well as reported by both themselves and their

parents when compared with national norms for key standardized instruments used in the screening. Nevertheless, parents reported short boys showed poorer social and academic competencies and greater behavioral problems than boys in the general population, but these differences were modest. The behavior profile of girls was indistinguishable from that of girls in the general population.

The studies by Vance and Sandberg were conducted under very different circumstances, yet the findings are quite similar: short stature, in and of itself, does not appear to be associated with clinically significant disruptions of psychological functioning. These 2 studies do not exclude the possibility that there are children with particular medical conditions that have short stature as 1 feature (eg, bona fide GH deficiency [GHD], TS) who are experiencing significant academic or psychological problems. This possibility was highlighted in the next presentation.

The third speaker, Dr. Brian Stabler of the University of North Carolina at Chapel Hill, summarized baseline data from the Genentech-sponsored, 4-year longitudinal study of academic achievement and psychosocial adjustment of a different clinical population: children receiving GH therapy (n=194). Specially trained nurses administered questionnaires and psychometric tests to parents and patients at several endocrine centers around the country. One in 5 children in this group (GHD, TS, and idiopathic short stature [ISS] diagnoses) were experiencing academic achievement problems, which is significantly higher than is observed in the general population. He also stated that behavior problem scores, as reported by a parent on a standardized behavior checklist, were elevated relative to norms among those children diagnosed as either GHD or idiopathic short stature. Girls with TS who were receiving GH therapy did not show elevated behavior problem scores. Both the GHD and TS groups (but not those with ISS) showed poorer social competency than a normative sample as measured by parent questionnaire. The finding that children typically came from well-functioning families (as assessed by another standardized questionnaire) of high socioeconomic status suggests that the problems observed are not likely attributable to factors related to demographic background.

In a separate study of adults with a history of GH therapy during childhood, Dr. Stabler reported that individuals with multiple pituitary hormone deficiencies (MPHDs; n=20) showed a muted cardiovascular response (ie, heart rate, systolic and diastolic blood pressure) to psychological stress (public speaking in this case). Those with isolated GHD (IGHD; n=5), however, functioned like short healthy comparison subjects (n=25). Those with hormone deficiencies were also different in their personality from short healthy adults: "neuroticism" (as measured by the NEO Personality Inventory) was higher in both those with IGHD and MPHD and "extraversion" was lower in the MPHD group. Finally, the MPHD group was significantly less assertive (on the Rathus Assertiveness Schedule) than short healthy adults, whereas the IGHD group was not. Small sample size in the IGHD group (n=5) limits the generalizability of the conclusions related to this subgroup. Detailed findings from this study have recently been published (Stabler B, Turner JR, Girdler SS, et al. *Clin Endocrinol* 1992;36:467).

Dr. Stabler explained how these findings emphasize the importance of comprehensive, multidisciplinary care for individuals with pituitary hormone deficiencies. Short stature by itself did not appear to be the primary factor explaining these results. Some other, as yet unspecified, factor was suggested as being responsible for the poor behavioral and social adjustment, such as a neuroendocrine imbalance.

Dr. Joanne Rovet of the Research Institute at the Hospital for Sick Children in Toronto described a postal survey that assessed the psychological benefits of GH therapy in TS (n=46). This ongoing longitudinal study includes 11 centers across Canada and is the only one to maintain a non-GH-treated control group (n=40) through to final height. Some of the findings collected up to this time (1.5 years into the study) include: problems of cognitive function that have repeatedly been demonstrated in girls with TS despite average intelligence; problems of sustaining attention in childhood; particular problems in the academic domain of mathematics; poorer social competencies and somewhat higher than expected levels of hyperactive-like symptoms. One and one half years after GH therapy was initiated, changes were observed in the following areas compared with the non-GH-treated group: decrease in hyperactive-like symptoms; *poorer* math achievement (an unpredicted and unexplained finding); improved social relations, popularity, and self-esteem. There was a trend for improvements in growth velocity with GH to be associated with a reduction in behavioral problems and improved social relations with peers.

These studies of very different nonclinical and clinical populations of children, adolescents, and adults with short stature demonstrate that height by itself may not be the essential factor determining how short individuals function behaviorally, emotionally, or academically. Instead, it may be a particular underlying medical condition–of which short stature is a feature–that may provide a far greater explanation of the variability in psychosocial functioning. The possibility that stature, by itself, predicts behavioral outcomes to only a small degree brings into question the justification of providing GH therapy to all short children to improve psychosocial adjustments. These data allude to the complex interaction between statural deficits, social behavior, and cognitive functioning in short children. Further study of these factors will help to clarify our understanding of such relationships.

Sleep, Growth Hormone Secretion, and Short Stature

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Considerable investigative effort has been directed toward studying the relationship between physiologic growth hormone (GH) secretion during waking and sleeping hours and growth. Much of this effort has concentrated on children with growth hormone deficiency (GHD) and idiopathic short stature (ISS), but sleep patterns and GH secretion in normal adults and GHD adults have also been reported.

ONTOGENY OF SLEEP

Sleep appears in virtually all mammalian species, yet we do not understand why we sleep, nor do we know how to measure the outcome of sleeping. We describe sleep by recording its periodicity and its occurrence with respect to the 24-hour light-dark cycle (or circadian rhythm). Periodicity varies in humans such that the neonate may have several sleep-wake cycles during the 24-hour period while most adults have 1 sleep-wake cycle. Adaptation to the light-dark cycle occurs in infants after 2 to 3 months, but the length of time it takes to adapt to sleeping predominantly in the dark phase of the light-dark cycle is variable. In the mature adult it appears that an endogenous "biological clock," with a periodicity of approximately 25 hours, is operative and influenced by external cues serving to keep us on a 24-hour cycle length. It is unknown whether the neonate already has such an endogenous clock.[1-5]

SLEEP STAGING

Sleep (stages 1 to 3) is staged by electroencephalography (EEG). Electrode placements aid in detecting eye movements (electro-oculography, EOG) and heart rate (electrocardiography, ECG). Using these recordings, the sleep EEG is divided into 2 major phases: rapid eye movement (REM) and non-REM sleep. In REM sleep, there may be increased heart rate (detected by ECG), increased eye movements (detected by EOG), and EEG patterns that are distinctly different than non-REM sleep. Dreams often occur during REM sleep.

In non-REM sleep, there are 4 distinct stages. The last 2 stages (stages 3 and 4) are characterized by the presence of low-frequency, high-amplitude wave forms lasting for extended periods. These stages are called slow wave or delta sleep. Stage 1 sleep is often described as light sleep and is a transition to the more clearly defined stage 2 sleep. Stage 1 is short-lived, usually lasting less than 10% of the total sleep period. Stage 2 sleep is characterized by the presence of clearly defined wave patterns, eg, sleep spindles and K-complexes. The total duration of stage 2 is often greater than 50% of total sleep.

Sleep is further defined by a characteristic transition from light sleep, stage 1 through stages 2, 3, and 4, followed by a period of REM sleep. This non-REM/REM cycle repeats itself throughout the typical night's sleep, although all of the non-REM stages need not occur before a period of REM ensues.

Human sleep stages vary from infancy through childhood to adulthood. Roffwarg et al[6] reported that newborn infants spend nearly 16 hours a day asleep, with half of the sleep being REM sleep. The duration of REM sleep steadily decreases, as does the total sleep period, with age, such that an adolescent sleeps an average of 8 hours a day and adults 50 to 90 years of age sleep an average of <6 hours. After an initial increase in the first decade of life, non-REM sleep time declines from 6.5 to 7 hours to <5 hours in the 50-to-90-year age group. The percentage of non-REM sleep that consists of delta sleep (stages 3 and 4) declines to nearly zero in the latter age group.

SLEEP-PROMOTING FACTORS (SUBSTANCES)

The discovery of episodic hormone secretion led to an increased understanding of circadian rhythms.[7-9] Sleep-associated rises of GH led to the speculation that sleep and sleep-onset may be influenced by such nocturnal GH elevations. These hypotheses were later proven to be incorrect through research on the causes of sleep, using animal models, during the past 10 to 15 years. Reports have supported speculations that there may be endogenous substances that either

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induce sleep or set into motion a sequence of events leading to sleep.[10,11] Such substances found in the central nervous system (CNS) are short polypeptides (nonapeptides) called delta sleep-inducing peptides (DSIPs) based upon their ability to induce delta (slow wave) sleep (stages 3 and 4). DSIP is a glycoprotein. The exact sequence of glycose moieties may vary, but the peptide portion appears relatively constant. DSIP is similar to the peptidoglycan sequences found in bacteria cell walls known as muramyl peptides.[12,13] Further studies have revealed that DSIPs, given orally to newborn rats, circulate intact in the blood. Immunoreactive DSIPs can be found in the CNS and some peripheral organs of mammalian species.[14,15] In humans, DSIPs have been found in breast milk, with a circadian secretion pattern consisting of an afternoon peak and an early morning trough.[14]

Other substances apparently have the same effect as DSIPs in promoting sleep. The link with DSIPs could be a common or shared cellular effect that promotes the release of lymphokines. Three major lymphokines, tumor necrosis factor (TNF), interleukin-1B (IL-1B), and interferon-L2 (IFN-L2) have sleep-promoting effects, causing delta sleep (stages 3 and 4).[12,13,16] IL-1B has been shown to release GH in animals. Another substance proposed to have a causal relationship with sleep-onset is prostaglandin D_2.[12]

SLEEP AND GROWTH HORMONE SECRETION

Many investigators have described the relationship of sleep and GH secretion. These studies have demonstrated that when sleep—especially delta sleep (stages 3 and 4)—is interrupted, GH secretion is diminished. Despite these observations, it remains unclear whether sleep and GH secretion have a causal interrelationship.[16-17]

GH may be secreted spontaneously during waking hours, during stress, and following provocative stimulation. The mechanism of GH secretion under these circumstances does not involve sleep, although children are often sleepy after administration of clonidine.

This observation led us to evaluate children being challenged with clonidine by monitoring their EEGs.[18] Preliminary data in 12 children with ISS demonstrated the simultaneous occurrence of GH release and EEG-defined sleep after oral clonidine (0.1 mg/m^2). In 8 of the 12 subjects, EEG-documented delta sleep developed. Their peak GH responses occurred at the same time as the other children who fell asleep but did not enter stage 3 or 4 sleep. The absence of delta sleep in the latter group did not prevent GH secretion, suggesting that neither GH secretion nor delta sleep is the prerequisite of the other.

Finkelstein et al,[19] Prinz et al,[20] and others have described an age-related decrease in GH secretion. Older adults also may have less delta sleep (Table 1).[21] This supports the concept that GH secretion and delta sleep are as closely related in adulthood as in childhood and adolescence.

Sleep and Growth Hormone Deficiency

Orr and colleagues[22] were among the first to describe sleep in children with GHD. They concluded that GHD children, ages 6 to 8 years, had more delta sleep than older GHD children, ages 14 to 16 years.

Our studies in GHD children suggest differences in stage 1, stage 3, and REM sleep as compared with normal children, but these differences were not statistically significant. We reevaluated these children after GH therapy was instituted and observed that stage 3 sleep decreased significantly

Table 1
Sleep in GHD and ISS Children

Study	Diagnosis	Age (Yr. Mo.)	Sleep Stages (% Total Sleep Time)						Wake
			1	2	3	4	3+4	REM	
Wu/Thorpy[24]	ISS (n=6)	4.10 - 16.6	6.9	45.7	10.3	16.4	(26.7)	20.3	18.0
	GHD (n=7)	6.3 - 10.5	9.7	41.0	10.0	19.7	(29.7)	19.5	1.0
Astrom/Lindholm[21]	GHD (n=8)	18.8 - 28.2	6.6	62.4	7.3	5.8	(13.9)	13.4	4.5
Prinz et al[20]	Normal males								
	(n=14)	23.0 - 28.0					(22.9)		
	(n=16)	58.0 - 82.0					(10.0)		
Williams et al[3]	Normal females	6.0 - 9.0[a]	2.3	47.8	3.1	16.8	(19.8)	29.3	0.7[b]
	Normal males	5.0 - 9.0[a]	2.3	47.9	3.6	18.5	(22.2)	27.3	0.3[b]

a) 6.0 - 9.0 year group differed from an older group (10.0 - 12.0), but the difference did not affect comparisons with other studies.[3] b) Calculated from data in Williams et al.[3] REM, rapid eye movement; ISS, idiopathic short stature; GHD, growth hormone deficiency.

($P<0.05$), while total delta sleep (stages 3 and 4) was unchanged.

Astrom and Lindholm[21] reported that delta sleep is decreased in adults with GHD. These adults, ages 18 to 28 years, had significantly decreased stage 4 sleep. Stage 3 sleep was reported to be approximately 7% of total sleep time. This percentage is comparable to that reported by Taylor and Brook[23] for non-GHD *children* and our data for GHD and ISS *children* (pretreatment, see Table 1).[24-26] Astrom and Lindholm further reported no significant differences in the amount of REM sleep corrected for the duration of sleep as compared with age-matched controls.[21]

Astrom et al[27] conducted similar studies in 8 GHD adults, ages 20 to 30 years, and found no change in delta sleep after GH therapy with increased REM and decreased stage 1 and stage 2 sleep. These data suggest that GH may exert its influence on sleep irrespective of delta sleep.

Sleep and Idiopathic Short Stature

Studying sleep and GH secretion in children with ISS provides an opportunity to evaluate this interrelationship in subjects with normal GH secretion in response to stimuli.

Preliminary data from ISS children reported by Taylor and Brook[23] indicate marked abnormalities in sleep and sleep stages. Their subjects, however, were diagnostically heterogeneous, (eg, genetic short stature, poor nutrition, psychosocial dwarfism, and constitutional delay of growth and puberty). In the subset with psychosocial dwarfism, stage 4 sleep was significantly decreased. REM sleep increased significantly in the subsets with psychosocial dwarfism and genetic short stature. One subgroup of children with severe short stature and behavioral problems (psychosocial dwarfism type 2) had significantly increased waking time. No details on sleep stages were reported, thus comparison with other data was not possible.

Table 2 summarizes our data in GHD and ISS children. Comparable results are demonstrated for REM and sleep stages 1 through 4 for the 2 groups. The percentage of stage 3 sleep in ISS and GHD children was comparable to the percentages reported by Astrom and Lindholm[21] for young GHD adults. The percentage of stage 3 sleep was significantly higher than that found in normals of the same age range as reported by Williams et al[3] (see Table 1). Our data further show significantly different percentages of waking time between GHD and ISS children (1.0% vs 18.0%, respectively). These observations, along with the reports of others, suggest an association of short stature, neuroregulatory dysfunction of sleep, and GH secretion.[23]

GH Secretion and Delta Sleep

To test the hypothesis that GH secretion and delta sleep are interdependent, we treated 7 patients with GHD and 11 patients with ISS, recording sleep before and after GH therapy.[26] Five ISS children served as controls. The preliminary results are shown in Table 2. The basic sleep stages, REM cycles, and total sleep times are comparable in the 3 groups. Of particular interest is the similarity of stage 3 sleep in all 3 groups *before* GH therapy. After therapy, there was a significant decrease in stage 3 sleep in the GHD and treated ISS groups ($P<0.05$ and $P<0.01$ respectively). The decrease in stage 4 sleep for the treated ISS group was not statistically significant.

These preliminary data suggest an interrelationship between exogenous GH and delta (stage 3) sleep. If a sleep-inducing substance such as DSIP is the mechanism for sleep induction and GH release in humans, our data suggest a specific feedback loop triggered by exogenous GH affecting delta sleep. While stage 3 sleep decreased after GH therapy in the treated ISS group, this same group had no demonstrable decline in GH secretion as determined by peak GH concentrations, mean GH levels, and GH secretory rates during sleep when tested 48 hours after the last dose.[28]

The association of GH secretion with sleep appears to be as complex as sleep itself.[8] Careful investigation in children and adults, including normal, ISS, and GHD subjects, is needed to examine age-dependent changes in sleep and GH secretion. Such research will help to elucidate the physiology of sleep and its interrelationship with GH secretion.

Table 2
Sleep Stages (% Total Sleep Time)[24,25]
Shown As Before/After GH Therapy

Diagnosis	1	2	3	4	REM
GHD (n=7)	9.7/11.2	41.0/41.4	10.0/7.5*	19.7/20.3	19.5/17.9
ISSRx (n=11)	4.0/6.3	38.2/47.7	10.0/3.7*	33.0/22.2	15.0/19.4
ISSC (n=5)	3.2/6.6	53.6/50.7	8.0/8.0	22.3/25.2	12.8/12.3

GHD, growth hormone deficiency; Ages 6.3-10.5 (yr.mo). ISSRx, idiopathic short stature, treated; Ages 6.7-11.6 (yr.mo). ISSC, idiopathic short stature, control; Ages 6.0-10.3 (yr.mo). * $P<0.05$.

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Abstracts From the Literature

Aggressive Surgical Management of Craniopharyngiomas in Children

Hoffman et al, from the Hospital for Sick Children in Toronto, report 14-years experience in total excision of craniopharyngiomas in 50 children (22 girls and 28 boys, from 1 year 10 months to 17 years 7 months in age). Headache with a duration of 2 weeks to 4 years was the most common presenting complaint (68%). Thirty-three patients (66%) had some endocrine abnormality at presentation (14%, hypothyroidism; 40%, short stature; 24%, diabetes insipidus; 18%, obesity; and 14%, delayed secondary sexual development). One patient presented with precocious puberty. Visual abnormalities were present in 30% to 60%, with 48% having a field defect, the most common being bitemporal hemianopia.

Computed tomographic (CT) evidence of tumor calcification was observed in all 50 patients. Eighty percent of the tumors had some form of cyst formation. Sellar enlargement and/or blunting of the dorsum sellae was noted in 40%. Half the tumors were prechiasmatic. Hydrocephalus was present in 24 of the 50 patients at the time of surgery and in 74% of the patients with retrochiasmatic tumors. The most common surgical approach was right frontal craniotomy. Forty-five patients, or 90%, were considered by the surgeon to have undergone total tumor excision at the time of surgery.

Follow-up was obtained on 46 patients. One died in the immediate postoperative period, and 2 others died 9 years after initial surgery. Follow-up was from 1 to 14 years and 39% for at least 5 years. Thirty-four percent (16) have experienced tumor recurrence, a third of which were asymptomatic and discovered on routine neuroimaging. Eight presented with headaches, 5 had deterioration in visual acuity, and 1 had an increased need for desmopressin. Among 13 patients with tumor recurrence, 5 had normal postoperative CT findings, but 8 demonstrated either calcification or residual tumor.

Nine had improvement in visual fields, but 16 of those who had no field defect before surgery had deterioration of visual fields. Endocrine deficiencies were observed in all 46 follow-up patients postoperatively. Over 90% required desmopressin, 89% cortisone, 83% thyroid hormone, 31% sex steroids, and 20% growth hormone. Seventy-four percent required a combination of thyroid hormone, cortisone, and desmopressin. Fifty-two percent were obese at follow-up, but almost 30% of these had been obese prior to surgery.

Twenty-seven children had a formal psychometric evaluation at follow-up. Twenty-six of 27 had intelligence levels at or above average levels. However, memory was impaired in 16 of the 28 children tested. Twenty-four of 39 assessed for educational status were attending regular school.

Quality of life was assessed by categorizing patients into 3 groups based on morbidity. Those in the first group, or those with the "good quality of life," had no tumor recurrence or, if the tumor recurred, it was adequately managed with surgery. In addition, these patients had good control of their endocrine deficiencies and were attending or had attended regular school, and displayed no behavioral or eating disturbances. Sixty-four percent of patients fell into this category. The severely handicapped group included patients with unstable tumor recurrence and poorly controlled endocrine status. They were not attending school because of behavioral problems or major psychological disturbances. Only 9% fell into this group. The remaining 27% fell into the intermediate group.

Hoffman HJ, De Silva M, Humphreys RP, et al. *J Neurosurg* 1992;76:47-52.

Editor's comment: *This is an interesting and very well compiled follow-up report regarding the outcome of microsurgical management of craniopharyngiomas evaluated by CT. The data have been carefully assessed and should provide useful information for pediatric endocrinologists who are often responsible for diagnosing this tumor and who need to discuss the outcome and prognosis with their patients and their families. It is interesting to note that radiation therapy was used only in patients with tumor recurrences. In 1992 most patients will receive radiation in addition to surgical therapy. Therefore, statistics using data from combined therapy should be improved over those presented here.*

William L. Clarke, MD

Binding Protein for Human Growth Hormone: Effects of Age and Weight

The authors studied the age-related changes in serum levels of high-affinity growth hormone-binding protein (GHBP) measured by gel chromatography on a long (100 cm) column of Sephacryl S200. This GHBP is considered to be identical to the extracellular portion of the hepatic receptor to growth hormone (GH). The method measures the 85-kd complex containing the GHBP, after addition of ^{125}I-labeled human GH of the 22-kd type in the serum to be studied. The results are expressed as the percentage of radioactivity eluting in the 80- to 90-kd range.

Sera from 250 normal infants and children were studied. GHBP was very low in cord sera, with an average of 3.3% ± 0.7%, and stayed near this level up to age 2 months. Then it sharply increased during infancy and reached 12.7% ± 3.9% at 18 to 24 months of age. Further increase during childhood was slower, with the mean level after age 18 years attaining 19.7% ± 7.1%, and a wide range of individual values between 7% and 40% in children ages 7 to 18 years, with no obvious change at puberty. There was no difference between females and males at any age.

Correlation with age was significantly positive in the younger children (r=0.31, P<0.005) but below the level of significance in the older group (r=0.15). Correlations with height and weight were calculated. Only 2 significant correlations were found: a moderately positive correlation with weight expressed as standard deviations (SD) for age in the patients aged at least 2 years (r=0.42, P<0.0001), and a weak negative correlation with height SD for age in older children (r=-0.17, P<0.025). Partial correlation analysis showed no change of the correlation with weight when height was excluded, and a small change of the negative correlation with height when weight was excluded (r=0.22).

From these data, the authors point out that nutrition affects GHBP levels. The high serum GHBP found in most overweight children is considered as likely to reflect an increased number of peripheral GH receptors. This could reflect the usually low serum GH concentrations in obesity, contrasting with normal levels of insulin-like growth factor 1 (IGF-1) and normal or sometimes increased growth velocity. The authors comment on other aspects of their results, and compare their data with those previously reported by other authors.

Holl RW, Snehotta R, Siegler B, et al. *Horm Res* 1991;35:190-197.

Editor's comment: *Among many studies of the main serum GHBP, this one seems of special value since it involves a great number of normal individuals from birth to adulthood, uses a most reliable technique, and calculates partial correlations in order to exclude the "pseudocorrelations" resulting from the physiologic relationships between age, height, and weight during childhood and adolescence. Not only the positive correlation with weight and probable correlation with nutritional status but also the negative correlation with the SD of height are reported. The study in newborns and infants suggests to the authors a relationship between GHBP, probably GH receptors, and the developmental switch from more or less GH-independent intrauterine growth regulations to GH-dependent postnatal growth mechanisms. The data appear to be a valuable contribution to the presently poor insight we have on early postnatal changes in the regulation of longitudinal growth.*

Jean-Claude Job, MD

2nd Editor's comment: *Dr. Paul Martha, Jr, and colleagues recently presented a paper at the American Pediatric Society/ Society of Pediatric Research (APS/SPR) meetings that supplements the data reported by Holl et al. For the purpose of broadening the perspectives regarding GHBP for our readers, the abstract by Martha et al is reprinted here from the program of the APS/SPR meeting.*

A LONGITUDINAL ASSESSMENT OF SERUM GROWTH HORMONE-BINDING PROTEIN IN NORMAL BOYS DURING PUBERTY

Recent studies suggest the high-affinity serum GHBP may serve an important role in regulating normal body growth in humans. Therefore, we evaluated the relationships among GHBP, linear growth, and GH secretion over time in normally growing boys (n=11). On 154 occasions over 4.0 to 5.1 years, a physical exam, height and weight measurement, 24-hour GH study, and serum GHBP measurement were performed. GHBP levels varied widely among the group and spanned a 12-fold range (40 to 504 pmol/L; coefficient of variation [CV] = 51%). However, individual subjects' values varied within much more narrow limits (intrasubject mean CV = 30%, mean range 3.1-fold, P<0.05). The individual subjects' overall mean GHBP correlated inversely with the overall mean 24-hour GH level (r=-0.61, P<0.05) and correlated directly with mean body mass index SD score (r=0.69, P=0.018). For individual subjects, GHBP did not correlate with growth velocity or age. GHBP levels (pmol/L) according to age (years) at the time of study were as follows:

Age	<11	11-11.9	12-12.9	13-13.9	14-14.9	15-15.9	16-16.9
GHBP	208±24	241±39	196±36	175±24	161±27	217±29	200±39

No statistical differences were detectable among groups, therefore these data indicate that although serum GHBP concentrations for each child fluctuate over time during puberty, they do so within relatively narrow limits more characteristic of the individual child than of the larger population. The maintenance over time of a positive correlation between GHBP to body mass index SD score and an inverse relationship to mean GH secretion level lends further support to the concept that these factors are intimately and inextricably interrelated to normal growth and development. The data do not support the existence of an increase in GHBP levels confined specifically to the period of active pubertal development.

Robert M. Blizzard, MD

Effects of Prolonged Growth Hormone Administration in Rats With Chronic Renal Insufficiency

Surprisingly, growth hormone (GH) administration to children and rats with chronic renal failure significantly increases the growth velocity (GV) over short periods. The long-term effect on GV and kidney anatomy, physiology, and histology is not yet known. Therefore, Allen et al sought to determine the long-term effects on rats. Four groups of young rats were placed in the study: GH-treated and untreated 75% nephrectomized rats and GH-treated and untreated sham-operated rats. GH 1.0 mg SC was administered tiw. The rats were examined at 9, 15, and 25 weeks. GH was administered during weeks 4 through 12. The following results were determined:

1. Uremic GH-treated rats grew significantly more than untreated rats. The lengths of treated uremic rats were comparable to untreated sham-operated rats at all times.
2. Sham-operated rats treated with GH were longer than untreated sham-operated rats.
3. Weights of uremic GH-treated rats equaled those of untreated sham-operated rats at 15 weeks.
4. Glomerular filtration rate was markedly and comparably reduced in all uremic rats. GH therapy did not affect glomerular filtration rate in either group.
5. Diminished food efficiency of uremic rats was not improved significantly with GH treatment.
6. Both mean glomerular area and sclerotic index were increased in GH-treated rats.
7. Mortality from chronic renal failure was 8 of 19 (42%) in uremic GH-treated rats versus 4 of 13 (31%) in untreated uremic rats.

Allen DB, Fogo A, El-Hayek R, et al. *Pediatr Res* 1992;31:406-410.

Editor's comment: *Studies of this sort are very much needed to sort out the beneficial versus detrimental effects of GH treatment in children with chronic renal failure and those posttransplantation (*GGH *1991;7[2]:13-14). Collaborative efforts among several centers are in progress to determine the effects of long-term GH treatment in chronic renal failure. In the meantime, GH should not be used for growth retardation in renal disease unless under an approved Investigational Review Board (IRB) protocol.*

Robert M. Blizzard, MD

Growth of Infants With Neonatal Growth Hormone Deficiency

There are limited data regarding the growth patterns of infants with neonatal growth hormone deficiency (GHD), and differences of opinion exist regarding the need for growth hormone (GH) to produce normal growth in the first 6 months of life. The authors studied 15 patients (8 males, 7 females) with GHD as well as other tropic hormone deficiencies in an attempt to answer this question. The patients were categorized as having GHD in the newborn period because of the presence of at least 1 of the following in association with GHD: hypoglycemia (13 of 15), micropenis (7 of 8 males), and/or jaundice (13 of 15). Breech delivery occurred in 5 of the 15.

Five had a birth length less than 2 standard deviations (SD) below the mean for gestational age. The mean birth length of the 15 was -1.5 SD below the normal average length. Eight patients had a growth curve with a downward deviation from birth onward, and 7 had no marked lateral deviation from the normal percentile curves up to 9 months.

The conclusion made was that the data are compatible with the hypothesis that (1) some infants with neonatal panhypopituitarism do not have total GHD at birth but develop such deficiency in the ensuing months. In support of this, 2 infants had shown peaks of normal GH release to provocative tests shortly after birth, but the peaks decreased later; (2) GH is necessary for growth immediately after birth; (3) it is uncertain whether, on the basis of the data presented, GH plays a part in prenatal growth; and (4) the ICP (infancy-childhood-puberty) growth model is dependent upon the presence of GH throughout all phases and is not independent during the infantile phase, as postulated by some clinical investigators.

Wit JM, van Unen H. *Arch Dis Child* 1992;67:920-924.

Editor's comment*: These data and conclusions are confirmatory as they support, in part, conclusions made some years ago. Brasel et al (*Am J Med *1965;38:484) reported that 39.5% of 39 patients with idiopathic GHD had growth failure during the first year of life. Of the 36 infants born at term, only 4, or 11%, had birth weights less than the third percentile, which is in contrast to the data of Wit and van Unen. Brasel et al concluded that GH was necessary for growth in the first year of life but probably not necessary in utero. The latter also is deducible from the studies of GHD infants born to GHD mothers where the infants are of normal birth weight and length. Interestingly, the GH insensitive patients of the Laron-type often are small at birth. Laron (*Adv Intern Med *1984) reported that 10 of 16 were more than 2 SD below the mean birth weight of normals. These data suggest that absence of the pituitary receptor may be more important in normal uterine growth than GH itself.*

A clinical point made by Brasel et al, which is not appreciated by many, is that one third of 33 patients with adequate dental records had delayed eruption of the primary teeth, and 75% of 36 GHD patients with adequate dental records had delayed eruption of the secondary teeth.

Robert M. Blizzard, MD

Psychosocial Growth Failure: A Positive Response to Growth Hormone and Placebo

Boulton et al report their study of a double-blind placebo crossover trial of growth hormone (GH) in 7 children (3 males, 4 females, ages 3.6 to 11.6 years; bone age range of 2 to 9.5 years) with the diagnosis of psychosocial growth failure. Six of these children had a disorder of attachment dating from infancy with recurrent depression in 3. The other child had reactive depression from current family stress. All children were measured with a Harpenden stadiometer. Growth velocity and weight were converted to standard deviation scores (SDS). All children had heights <3rd percentile (-2 SDS), growth velocity <25th percentile (-0.09 SDS), and had been monitored at least 1 year at 3-month intervals. All were prepubertal at the start of the trial. GH secretion was measured at 20-minute intervals during the first 3 hours of sleep and the results analyzed using the PULSAR program. Dietary intake was assessed by computer analysis of 4-day food diaries.

Mean GH concentration during sleep was 10.9 ± 4.4 mU/L with a mean peak level of 19.6 ± 6.7 mU/L. All subjects had a maximum peak of 20 mU/L or greater. Mean peak interval was 147 ± 108 minutes. The mean (± SEM) insulin-like growth factor 1 (IGF-1) was 1.08 ± 0.31 U/mL. The mean (± SEM) SDS growth velocity prior to treatment was -2.32 ± 0.122, for the placebo period -0.6 ± 0.69, and for the GH treatment period +4.66 ± 1.88. Significant differences in velocity between each of the 3 periods were demonstrated by analysis of variance ($P<0.0001$). The greatest difference between growth velocities was between the pretrial and GH periods ($P<0.001$). The order of treatment did not affect the growth response. The mean (± SEM) IGF-1 did not change significantly during GH treatment (1.24 ± 0.34 U/mL at the end of treatment versus 1.09 ± 0.31 U/mL pretreatment). The mean daily food energy intake was similar for the trial, pretrial, and posttrial periods.

Boulton TJC, Smith R, Single T. *Acta Paediatr* 1992;81:322-325.

Editor's comment: *This is an interesting report, but it is not clear that the children studied had classic psychosocial dwarfism. While in their adverse environment, as defined by Powell et al, children with this syndrome often have reversible GH deficiency with abnormal GH responses to pharmacologic stimuli. GH secretion in the children in the present study was normal. Therefore, they were not shown to have GH secretory dysfunction. The authors acknowledge this, and suggest that the GH secretion and growth response of these children are similar to those of children with constitutional delay of growth. However, the presence of a significant placebo effect suggests that the intervention may have altered family dynamics in some manner. Even though these children do not necessarily fit the original criteria for the definition of psychosocial dwarfism, they clearly had psychological dysfunction and significant growth retardation that responded to GH administration. Thus, these children, and other similar children, may be potential candidates for GH treatment. Whether or not such treatment may alter their psychological status is left for speculation.*

William L. Clarke, MD

2nd Editor's comment: *The topic of psychosocial short stature (PSS) has been of great interest since we (Powell et al,* N Engl J Med *1967) reported a group of children with the syndrome who had reversible hyposomatotropism. Recently, I have written 2 reviews of this topic; the first in* Pediatric Endocrinology: A Clinical Guide, *edited by F. Lifshitz (1990), and the second in a text entitled* Bailliere's Clinical Endocrinology and Metabolism. *Growth Disorders, edited by J. Bierich (1992). These references are given for readers who may wish to read further concerning the topic.*

*The report by Boulton et al is of importance because of the response of depressed children with growth failure to pharmacologic doses of GH (1.2 U/kg/wk), which is significantly more than the physiologic replacement dose (0.3 U/kg/wk) reported by Fraiser and Rallison (*J Pediatr *1972;80:603) to not increase the growth of patients with PSS. As pointed out by the authors and by Dr. Clarke in his editorial commentary, these children are different from most children reported with PSS in that they secreted normal amounts of GH. The authors, unfortunately, did not comment on the behavioral characteristics of these children, except for depression. The children described by us and others with PSS often had polyphagia, polydipsia, and encopresis; ate and drank from bizarre places such as dog dishes, gorging themselves to the point of vomiting; and were emotionally rejected by their parents. Hopefully, Boulton et al will write a follow-up article or write a letter to the Editor of* GROWTH, Genetics & Hormones, *providing the psychological and emotional characteristics of the children reported and of their parents. The paper by Boulton et al is an important paper and we need to be able to place it in a better context in relation to other papers published on the topic.*

Robert M. Blizzard, MD

In Future Issues:

Fragile X Syndrome: Review and Current Status
by David L. Nelson, PhD

Prenatal Evaluation of Growth by Ultrasound
by Douglas Wilson, MD

The Use of Fluorescence in situ Hybridization to Identify Human Chromosomal Anomalies
by Beverly S. Emanuel, PhD

The Importance and Methods of Using Animal Models to Study Human Disease
by Robin M. Winter, MD

Relevance of Developmental Genetics to Human Malformations
by Golder N. Wilson, MD, PhD

Pituitary Evaluation and Growth Hormone Treatment in Prader-Willi Syndrome

Angulo et al evaluated the spontaneous growth hormone (GH) secretion and GH responses to clonidine, levodopa, and insulin-induced hypoglycemia in 11 obese and 4 nonobese Prader-Willi syndrome (PWS) patients, 1.5 to 15.5 years of age. Ten patients (3.7 to 15.5 years of age) were treated with GH at 0.1 mg/kg tiw for 6 months.

Integrated concentrations (ICs) of GH using a Cormed-Kowarski constant withdrawal pump, with the specimens being collected over 24 1-hour periods, ranged between 1.0 to 2.1 μg/L, which the authors state was markedly deficient in all.

The responses to insulin, clonidine, and levodopa were variable. Only 1 patient had a serum GH level above 8.0 μg/L, following 150 $\mu g/m^2$ po of clonidine. Values of serum GH following levodopa were above 8.0 μg/L in 3 patients (12.6, 11.4, and 11.4 μg/L). The response to insulin (0.1 U/kg IV) was 8 μg/L or above in 8 patients. The authors conclude that GH deficiency probably was present in all patients. The somatomedin-C (Sm-C) determinations were <1.0 U/mL and compatible with GH deficiency in 9 of 15 patients. Bone age (BA) determinations were not less than -2 standard deviations (SD) for chronologic age (CA) in any patients.

GH treatment over 6 months increased the mean growth velocity (GV) from 2.0 ± 2.3 cm/yr to 5.3 ± 1.5 cm/yr. GV doubled in all patients except in a 15.5-year old male with a BA of 14.5 years, a BA at which the average male has only 5% of his ultimate height yet to be gained. The patients gained little weight. Sm-C levels routinely increased to above 1.2 U/mL with a mean of 1.5 ± 0.2 U/mL.

The authors conclude that "short stature associated with obesity, hypotonia, decreased energy expenditure, delayed skeletal maturation and failure to respond to GH stimuli makes PWS children potential candidates for GH therapy. Further studies, however, are necessary to investigate the safety and long-term effects of this form of therapy."

Angulo M, Castro-Magana M, Uy J. *J Pediatr Endocrinol* 1991;4:167-172.

Editor's comment: *The authors performed a well-designed study. The data provide both the stimulation and basis for future investigation of GH secretion and response to GH therapy by PWS patients. The data, as presented, support the concept that these patients may have GH deficiency. Responses of GH release secondary to pharmacologic testing with 3 stimulating agents certainly appear to be low. Seven of the patients had no peak of GH >8.2 ng/mL in any of the tests (insulin, clonidine, levodopa). Only 2 patients in the entire group of 15 had a value >8.0 ng/mL in more than 1 of the 3 tests. The IC values of GH were <2.1 ng/mL in all which logically prompts one to suspect GH deficiency. Unfortunately, the authors have not provided data of IC for children of normal size. Their control data are taken from the literature, which is always suspect because of the variability of studied groups and the different assays employed, and from studies they have published for children with delay of growth and pubertal development (*J Pediatr Endocrinol *1989;3:225). In that study, the IC of GH for 44 of 49 short patients was 2.2 ± 0.6 ng/mL. Although some investigators have shown that children with similar short stature have normal ICs of GH, as compared with children of normal size, others have not. Therefore, Angulo et al need to publish concerning their study controls of normal size to diagnose GH deficiency in the PWS patients by using the IC of GH. The response to GH treatment by PWS patients is encouraging, although the study of GH treatment was for only 6 months.*

It must be noted that the dose of GH used (0.1 mg/kg tiw) is a pharmacologic dose, and may be expected, therefore, to often produce an increased GV in both children of normal and short stature. However, the fact that increased growth rate in PWS patients results from pharmacologic doses does not diminish its potential therapeutic application. I use the word "potential," as the effect on final height is the ultimate criterion for GH treatment in these patients. The authors appropriately conclude that further studies are necessary to investigate safety and long-term effects. All of us will follow with interest the subsequent periods of treatment.

Robert M. Blizzard, MD

Effects of Insulin-Like Growth Factor on Linear Growth, Head Circumference, and Body Fat in Patients With Laron-Type Dwarfism

Five children with Laron-type growth hormone insensitivity syndrome (LTS) were treated with recombinant insulin-like growth factor 1 (IGF-1) injected SC once daily at an initial dose of 150 μg/kg/d. The dose then was adjusted according to serum IGF-1 concentration. Striking changes in growth occurred from the first month, with a growth velocity corresponding with 8.8 to 13.6 cm/yr. Body fat, measured by subscapular skin-fold, decreased in the same time.

In 2 of these LTS patients, continuation of treatment for 10 months induced important morphologic changes, characterized by maximal limb growth and, unexpectedly, a striking and early increase of head circumference, even at age 13 to 14 years. There were no undesirable side effects, particularly metabolic. This suggests to the authors a possible effect on brain growth. Though preliminary, these results are encouraging for long-term treatment of LTS and probably other growth hormone insensitivity syndromes.

Laron Z, Anin S, Klipper-Aurbach Y, et al. *Lancet* 1992;339: 1258-1261.

Editor's comment: *This is the second report that IGF-1 increases the growth of LTS individuals. The first was by Walker et al (*N Engl J Med *1991;324:1482). IGF-1 has the potential to be as important a therapeutic agent as growth hormone. We can anticipate in the next few years reading many studies designed to test the effectiveness of IGF-1 in metabolic disorders as well as in growth disorders. Fortunately, it has been demonstrated that IGF-1 can be given to humans with minimal concern of producing hypoglycemia from its insulin-like action. (Takano, et al.* Growth Regulation *1991;1:23-28.)*

Jean-Claude Job, MD

Expression and Regulation of IGF-1 in Cartilage and Skeletal Muscle

Isgaard presents a mini-review of this topic of great importance. The major questions to be answered relate to the roles that growth hormone (GH) and insulin-like growth factor 1 (IGF-1) play individually and collaboratively on the acute and long-term growth of cartilage and skeletal muscle.

Because of the length and complexity of the review, only the introduction and concluding remarks are reproduced here, along with a brief editorial comment. Those who are interested, and there should be many, will wish to obtain and read the entire article.

INTRODUCTION

A number of studies have demonstrated that both GH and IGF-1 have important roles for skeletal growth. Although IGF-1 was originally considered to be produced mainly in the liver, it is now generally recognized that IGF-1 is synthesized in numerous organs and tissues of many animal species. It appears that IGF-1 synthesis in most tissues is regulated by GH, and autocrine and paracrine functions of IGF-1 have been suggested as important components of GH action. Moreover, several studies have revealed enhanced expression of IGF-1, both on the messenger and protein level, during tissue regeneration and repair. The present review is mainly focused on recent studies of IGF-1 and their relevance to possible in vivo effects during growth and regeneration of skeletal tissues.

CONCLUDING REMARKS

Accumulating evidence indicates an important role of IGF-1 in the promotion of tissue growth and repair. However, the relative importance of autocrine/paracrine versus endocrine actions remains to be fully clarified and matters of opinion differ. It has been suggested that the autocrine/paracrine actions of IGF-1 play a minor role compared to endocrine effects, which would account for approximately 80% of the total accumulated GH-IGF-1 dependent postnatal height in humans. These investigators base their assumption on the fact that local administration of GH into the growth plate or via the arterial blood supply of one hindlimb of hypophysectomized rats produces only 12% to 22% of the maximal growth that can be achieved with systemic administration of GH. However, it is improbable that the conditions during these experiments are comparable to those when GH is administered systemically. Therefore, it is highly unlikely that local administration of GH could produce effects of the same order of magnitude as systemically administered GH. It would also be reasonable to assume that locally produced IGF-1 is of importance during tissue hypertrophy and repair, when high levels of IGF-1 mRNA are expressed without a concomitant rise in circulating IGF-1. Moreover, the stimulatory effect of locally administered GH on the growth plate of hypophysectomized rats was completely abolished if antibodies to IGF-1 were coinfused with GH. This observation argues for the fact that locally produced IGF-1 is essential for the growth-promoting effect of GH in vivo.

The role of GH in the regulation of IGF-1 expression in peripheral tissues other than the growth plate is less clear. IGF-1 synthesis appears to be regulated by GH in most tissues, since the levels of both IGF-1 and IGF-1 mRNA decrease in a large number of tissues after hypophysectomy. On the other hand, during tissue regeneration following injury, increased expression of IGF-1 has been demonstrated in the regenerating tissue, both in intact and hypophysectomized animals. It is conceivable that GH regulates the synthesis of IGF-1 in tissues during normal growth and development, in contrast to emergency situations such as tissue injury or loss of tissue, during which this GH dependence may be uncoupled. Precisely which are the factors that regulate the synthesis of IGF-1 during tissue repair have yet to be clarified.

Isgaard, J. *Growth Regulation* 1992;2:16-22.

Editor's comment: *This paper reviews the data known on the role of IGF-1 in cartilaginous and muscular growth and repair. In vitro, as well as in vivo, studies show that it is an important factor. However, the respective effects of endocrine GH-dependent and local paracrine/autocrine IGF-1 are not yet clarified, and the regulation of local IGF-1 by GH is still controversial. Some experiments quoted in this review, based on the expression of IGF-1 and the measurement of its mRNA in cartilage and muscle under influence of GH, suggest that the endocrine and/or GH-dependent effects are predominant under normal conditions. It can thus be speculated by Isgaard that GH regulates the synthesis of IGF-1 in tissues during normal development, in contrast to emergency situations, during which this dependence to GH may be uncoupled.*

Jean-Claude Job, MD

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